HOKKAIDO UNIVERSITY

Title	The impact of preoperative psychiatric intervention for postoperative delirium after major oral and maxillofacial surgery with free flap reconstruction
Author(s)	Nitta, Yukie; Sanuki, Takuro; Sugino, Shigekazu et al.
Citation	Journal of Stomatology Oral and Maxillofacial Surgery, 126(1), 102026 https://doi.org/10.1016/j.jormas.2024.102026
Issue Date	2025-02
Doc URL	https://hdl.handle.net/2115/95916
Rights	© 2025. This manuscript version is made available under the CC-BY-NC-ND 4.0 license https://creativecommons.org/licenses/by-nc-nd/4.0/
Rights(URL)	https://creativecommons.org/licenses/by-nc-nd/4.0/
Type	journal article
File Information	JORMAS-D-24-00446_R2.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Journal of Stomatology oral and Maxillofacial Surgery

The Impact of Preoperative Psychiatric Intervention for Postoperative Delirium after Major Oral and Maxillofacial Surgery with Free Flap Reconstruction

--Manuscript Draft--

Manuscript Number:	JORMAS-D-24-00446R2
Article Type:	Original Article
Keywords:	postoperative delirium; Risk factors; preoperative psychiatric intervention; oral and maxillofacial surgery; free flap reconstruction
Corresponding Author:	Kanta Kido, DDS,PhD Hokkaido University JAPAN
First Author:	Yukie Nitta, DDS, PhD
Order of Authors:	Yukie Nitta, DDS, PhD
	Shigekazu Sugino, MD,PhD
	Takuro Sanuki, DDS,PhD
	Masahiro Sugimoto, PhD
	Kanta Kido, DDS,PhD
Abstract:	Background: Postoperative delirium (POD) is a severe complication associated with various adverse outcomes, especially in older patients. Although the incidence and risk factors for POD have been explored in general surgery, they have not been fully elucidated. Early identification of high-risk patients and active preoperative intervention are considered essential for the prevention of POD. Recently, psychiatric consultation intervention have been shown to prevent delirium. This study investigated the effect of preoperative psychiatric interventions on preventing POD in our specific surgical context. Materials and Methods: This retrospective, single-centre observational study included 86 patients who underwent major oral and maxillofacial surgery with free flap reconstruction between 2016 and 2023. The effect of psychiatric intervention were compared between patients with and without delirium. Results: Preoperative psychiatric intervention did not reduce the incidence of POD. The incidence of POD was 29.1%. Univariate analyses showed no significant associations between POD and any clinical variables. Conclusion: There was no difference in the incidence of POD between patients who received preoperative psychiatric intervention and those who did not, and further investigation is needed to determine the efficacy of preoperative psychiatric intervention in the prevention of POD.

Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation

The Impact of Preoperative Psychiatric Intervention for Postoperative Delirium after Major Oral and Maxillofacial Surgery with Free Flap Reconstruction

Yukie Nitta[a], Takuro Sanuki[b], Shigekazu Sugino[c], Masahiro Sugimoto[d], Kanta Kido[a, *]

[a] Department of Dental Anesthesiology, Faculty of Dental Medicine and Graduate School of Dental Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

[b] Department of Dental Anesthesiology, Kanagawa Dental University, Yokosuka, Japan

[c] Department of Anesthesiology and Perioperative Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

[d] Institute for Advanced Biosciences, Keio University, Tsuruoka, Yamagata, 997-0052, Japan

*Address correspondence and reprint requests to:

Kanta Kido, D.D.S., Ph.D.

Department of Dental Anesthesiology, Faculty of Dental Medicine and Graduate School of Dental Medicine, Hokkaido University, Nishi 7, Kita 13, Kita-Ku, Sapporo, Hokkaido 060-8586, Japan

Tel: +81-117-064-336

Fax: +81-117-064-336

Email: k.kido.hkd@gmail.com

Manuscript (No author details)

Click here to access/download;Manuscript (No author details);Manuscript R2 (no author details).docx

Click here to view linked References

Abstract

Background: Postoperative delirium (POD) is a severe complication associated with various adverse outcomes, especially in older patients. Although the incidence and risk factors for POD have been explored in general surgery, they have not been fully elucidated. Early identification of high-risk patients and active preoperative intervention are considered essential for the prevention of POD. Recently, psychiatric consultation intervention have been shown to prevent delirium. This study investigated the effect of preoperative psychiatric interventions on preventing POD in our specific surgical context.

Materials and Methods: This retrospective, single-center observational study included 86 patients who underwent major oral and maxillofacial surgery with free flap reconstruction between 2016 and 2023. The effect of psychiatric intervention were compared between patients with and without delirium.

Results: Preoperative psychiatric intervention did not reduce the incidence of POD. The incidence of POD was 29.1%. Univariate analyses showed no significant associations between POD and any clinical variables.

Conclusion: There was no difference in the incidence of POD between patients who received preoperative psychiatric intervention and those who did not, and further investigation is needed to determine the efficacy of preoperative psychiatric intervention in the prevention of POD.

1. Introduction

Postoperative delirium (POD) is a severe postoperative complication after surgery, especially in older patients. According to DSM-5 [1], delirium is a confusional state defined by the acute onset of deficits in attention, awareness, and cognition that fluctuate in severity over time. Postoperative delirium is associated with multiple adverse outcomes such as prolonged hospital stay [2], higher costs [3], high morbidity, worsening of cognitive impairment [4], and increased in-hospital mortality [5].

Postoperative delirium can be classified into hyperactive, hypoactive, and mixed subtypes. Hyperactive delirium increases the risk of agitation and violent behavior due to the inability to maintain postoperative rest due to restlessness. In contrast, hypoactive delirium increases the risk of delayed bed release and aspiration pneumonia due to delayed detection due to lethargy [6].

The current literature reports that the incidence of POD after general surgery ranges from 36% to 40% [7]. Meanwhile, after major oral and maxillofacial surgery, including operations with free flap reconstruction, the incidence of POD was 11–37% [8, 9]. Although several perioperative risk factors have been reported, including older age [8, 10, 11], male sex [8, 11], tobacco consumption [8, 11], alcohol consumption [12], duration of surgery and anesthesia [8], blood transfusions [13, 14], neck dissection [12], and duration of ICU stay [10, 12], the risk factors have not been fully elucidated.

Early identification of relevant risk factors and appropriate intervention enable the prevention of approximately 40% of POD cases [7]. Early detection of high-risk patients and early active preoperative intervention is the key to reducing the risk and severity of POD. Accordingly, intraoperative and postoperative management and a multisystem approach have been required to prevent delirium [4, 7]. Recently, some preoperative approaches have been supported to reduce the incidence and duration of delirium in the ICU [15]. Psychiatric consultation intervention is one of the approaches used to improve psychiatric outcomes [16, 17]. In our hospital, preoperative psychiatric intervention is currently conducted before major oral and maxillofacial surgery with free flap reconstruction. However, to our knowledge, there have been no reports on preoperative psychiatric intervention for the prevention of delirium in this field or reports of its preventive effect.

The main purpose of this study was to investigate the effect of preoperative psychiatric interventions on

POD incidence compared without interventions after major oral and maxillofacial surgery with free flap reconstruction. In addition, we also examined the incidence and risk factors of POD in the same clinical setting.

2. Materials and Methods

This single-center, retrospective, observational study was approved by the Institutional Review Board of Hokkaido University Hospital (clinical study code 023-0465) and was conducted following the principles of the Declaration of Helsinki and its amendments. The Institutional Review Board waived the requirement for informed consent because comprehensive consent was obtained before general anesthesia.

2.1. Study population

Ninety-three patients who underwent oral and maxillofacial surgery with free flap reconstruction in the Department of Oral Diagnosis and Medicine or Department of Oral and Maxillofacial Surgery at Hokkaido University Hospital during the 8 years between January 1, 2016, and December 31, 2023, were comprehensively reviewed. The exclusion criteria were (1) incomplete medical records, and (2) unplanned reoperation within 5 days after surgery (Figure 1).

2.2. Surgical procedure, intraoperative and postoperative management

All surgical procedures were performed under general anesthesia. In all cases, tracheotomy was performed at the start of surgery and was followed by major tissue resection. Oral surgeons performed the tumor resection and neck dissection, while plastic surgeons performed the reconstruction. Under a microscope, a plastic surgeon reconstructed the defect with an appropriate microvascular free flap. The flap was harvested from the donor site and inserted into the wound, after which the operation was completed.

All patients were anesthetized using an inhalational anesthetic (1.5–2.0% sevoflurane or 4% desflurane) with narcotics (fentanyl and remifentanil) and a muscle relaxant (rocuronium). Patients were intubated orally or nasally before tracheostomy. In all cases, a gastric feeding tube was inserted before surgery. Mean arterial blood pressure (MAP) was monitored. Blood pressure was adjusted using one or more intravenous vasopressors as needed.

After the surgery, all patients were managed in the intensive care unit (ICU). In the ICU, patients were sedated with propofol, dexmedetomidine (DEX), or the combination of propofol and DEX and ventilated at the

discretion of the intensivist. Sedation was maintained with the patient under invasive mechanical ventilation for approximately 12 h. Sedation was reduced in the ICU if the patient was stable on postoperative day 1.

The patient was then weaned from ventilatory support and discharged from ICU back to the ward. All patients were kept on bedrest for 72 h postoperatively for flap healing. Mechanical methods of prophylaxis (such as graduated compression stockings and intermittent pneumatic compression devices) were used perioperatively to prevent deep vein thrombosis. Some patients were sedated with propofol and/or DEX as needed. For postoperative analgesia, patients were given fentanyl and/or non-steroidal anti-inflammatory drugs and/or acetaminophen as needed. Drugs were prescribed by a psychiatrist (e.g., suvorexant, ramelteon, quetiapine, haloperidol, or risperidone) when POD occurred. Although the patients diagnosed high risk of POD was observed more carefully by surgeons and nurses, most patients received standard monitoring in ICU and ward postoperatively.

2.3. Preoperative psychiatric intervention

The management of postoperative delirium in patients recieving surgery has been covered by national health insurance since 2020 in Japan. Before the year, whether preoperative psychiatric consultation for patients undergoing major head and neck surgery with reconstruction was requested or not depended on the surgeon’s decision. After 2020, almost of all the patients were consulted to psychiatry prepoperatively.

The psychiatrist assessed the patient's risk of POD and explained what POD was to the patient before surgery. The risk of POD was shared with the attending oral surgeons and ward nurses through the patient’s electronic medical record. Patients diagnosed by the psychiatrist as high risk for POD were prescribed psychiatric medications at the psychiatrist's discretion. The psychiatrist provided instructions to the attending oral surgeon on the medication regimen for the onset of POD. The psychiatrist, at their own discretion, provided postoperative follow-up commensurate with the patient's risk of POD and participated in the treatment of POD at the onset of POD. If surgeons or nurses suspected POD in postoperative patients who did not receive psychiatric consultation, they consulted the psychiatrists and followed their order. However, an explicit

guideline for prevention of POD has not been established yet, so that the treatment or medication including drug regimen or doses have depended on attending psychiatrists.

2.4. Study outcomes

The primary outcome was the effect of preoperative psychiatric interventions on the prevention of POD. The secondary outcomes were the incidence of POD and perioperative risk factors for POD.

2.5. Data collection

All patient data were collected from preoperative examination notes, medical charts, and anesthetic records.

Patient demographic characteristics include sex, age, body mass index (BMI), history of smoking (smoking for at least 2 years), history of alcohol consumption (estimated weekly ethanol intake of ≥200 ml), benzodiazepine use, American Society Anesthesiologists (ASA) physical status, age-adjusted Charlson Comorbidity Index (ACCI) [13], and comorbidities (hypertension, cerebrovascular disorder, diabetes, and mental disorder).

Preoperative data included preoperative psychiatric intervention, preoperative blood test results (albumin, hemoglobin, estimated glomerular filtration rate [eGFR], and C-reactive protein [CRP], neutrophil to lymphocyte ratio [NLR], and platelet to lymphocyte ratio [PLR]), and the number of remaining teeth.

Intraoperative data included operative time, anesthesia time, opioid use (amount of fentanyl and remifentanil), intraoperative blood loss, intraoperative urine output, the use of allogenic blood transfusion (red blood cell), intraoperative total balance, intraoperative blood test results (glucose and lactate), intraoperative arterial hypotension (mean arterial blood pressure <55 mmHg and ≥15 minutes), and maximum body temperature.

Postoperative data included the CRP level on postoperative day 1 and postoperative sedative use (the use or non-use of DEX in the ICU).

2.6. Diagnosis of POD

POD was diagnosed by a psychiatric physician consulted by attending oral surgeon or nurses when patients showed symptoms characterized by disturbance of consciousness and a change in cognitive capacity, the development of symptoms during a short period (hours to days), and fluctuation of mental status after the first postoperative day. This study did not distinguish between the subtypes of POD (i.e., hyperactive, hypoactive, and mixed types).

2.7. Statistical analysis

EZR version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) statistical software was used to analyze the relevant data. Propensity score matching was performed at a 1:1 ratio and was employed to address potential confounders related to age, sex, ASA, and benzodiazepine use to control effectively for common characteristics and variables between preoperative psychiatric intervention groups and no psychiatric intervention groups. We compared the patient background factors and perioperative factors using the Fisher's exact test between the 2 groups. In addition, we adopted some factors in our multivariate logistic regression analysis. The significance level was considered statistically significant for $p < 0.05$.

3. Results

3.1. Patient characteristics and psychiatric interventions: primary outcomes

Ninety-three patients met the inclusion criteria, and their charts were systematically reviewed. One patient was excluded from the analysis due to incomplete medical records and 6 patients were excluded due to reoperation within 5 days. A total 86 patients were included in the analysis (Figure 1). Table 1 shows the patient demographic data in both groups. 25 patients developed delirium, while the remaining 61 patients did not develop delirium. In psychiatric intervention group, 15 patients received pharmacological intervention with ramelteon or suvorexant. There was no significant incidence of POD in pharmacological intervention group and non pharmacological intervention group respectively (33.3% vs. 32.9%, p=0.96). Consequently, the incidence rate of POD was determined to be 29.1 % in this cohort of patients. Univariate analysis showed no difference in the occurrence of POD with or without preoperative psychiatric intervention (Table 1). Therefore, we used propensity score analysis to adjust for potential confounders. Based on age, gender, ASA, and benzodiazepine use, 64 patients were selected through propensity score analysis (1:1) to compare the 2 groups. Univariate analysis revealed significant differences in blood loss and total remifentanil dose between the 2 groups (Table2). Given the possibility that the intervention effect on the occurrence of POD was confounded by these factors, Binary logistic regression analysis was performed. Binary logistic regression analysis showed no significance between POD occurrence and POD, blood loss, and total remifentanil dose (Table 3).

3.2. Incidence and perioperative risk factors of postoperative delirium: secondary outcomes

Twenty-five patients (29.1%) developed POD. The onset of POD occurred at 1 to 4 days after surgery. In this study, 17 patients developed POD within 2 days postoperatively. Only 1 patient was diagnosed with hypoactive delirium by a psychiatrist. All other patients presented with symptoms of hyperactive delirium. Patients with POD were treated with psychiatric medications (quetiapine, haloperidol, risperidone) under the direction of a psychiatrist until their symptoms had been relieved. In all POD cases, the patient's delirium recovered rapidly without delay.

To examine the perioperative risk factors, univariate analyses was performed betweenx in POD groups and non-POD groups. Although age, smoking history, ACCI, and NLR each showed a tendency toward an

association with increased incidence of delirium, no preoperative, intraoperative, or postoperative parameters were identified as significant risk factors for POD in the univariate analysis in this study.

4. Discussion

In this study, we found that i) preoperative psychiatric intervention did not reduce the incidence of POD, ii) the overall incidence of POD was 29.1%, which is similar to the incidence reported in previous studies [10-12], and iii) none of the previously reported risk factors for delirium showed a significant association with the incidence of POD.

Recently, multi-component interventions have become the mainstay for managing POD, although medication is still essential [7, 16, 28]. Some studies have evaluated the role of proactive ICU rounding with psychiatry for surgical ICU patients and medical inpatients [16, 29, 30]. In recent years, there has been strong interest in the potential of psychiatric interventions to reduce the incidence and duration of delirium in surgical patients. The effects included the earlier identification of postoperative anxiety [30] and a shorter length of stay [16]. In contrast, few studies have evaluated the prevention of delirium. Choi et al. assessed the effect of postoperative ICU rounding with psychiatry on the incidence of delirium and found no significant association between postoperative psychiatric intervention and the incidence of POD [29]. They explained that the multifactorial etiology of POD is one of the factors that makes the prevention of POD difficult. There were two differences between our study and Choi et al.'s [29]. Firstly, in our study, the occurrence of POD was mainly assessed in the ward. Secondly, psychiatric intervention was initiated preoperatively. In our study, the psychiatrist examined and counseled the patient preoperatively, identified the patient's risk of POD, and shared it with other medical staff. Patients at high risk for POD were given medication preoperatively at the discretion of the psychiatrist. Postoperatively, patients assessed as high risk for POD were followed more carefully. The fact that the psychiatric intervention in our study was more generous than that reported by Choi et al., but still failed to reduce the incidence of POD suggests that further research is needed to reduce the incidence of POD.

Many studies have been conducted on the risk factors for POD in patients after major head and neck surgery [18, 19]. However, the risk factors have not yet been fully identified due to its complex morbidity [18]. In general, patients who have undergone major oral and maxillofacial surgery with free flap reconstruction have prolonged surgery and anesthesia, multiple surgical sites, considerable blood loss, prolonged postoperative ICU stay and bed rest to protect the anastomosed vessels, and restricted verbal communication due to tracheostomy.

Therefore, the incidence of POD may differ between patients treated with and without reconstruction [11]. Advanced age is the most crucial predisposing factor for POD [7]. However, previous studies evaluating increasing age as a risk factor for POD have reported diverse results. Choi et al. [10] and Ishibashi et al. [11] identified increasing age as a significant risk factor for the development of POD in univariable analyses. In contrast, Densky et al. identified increased age as a risk factor based on a multivariable analysis [8]. Meanwhile, increased age was not found to be a risk factor in studies by other investigators [9, 14]. In the univariate analysis of our study, increased age was not a significant risk factor for the development of POD. In a recent meta-analysis, Dong et al. concluded that advanced age was associated with a relatively low risk of POD after head and neck cancer surgery [18].

One meta-analysis suggested that male sex was also a risk factor for the development of POD after head and neck surgery [18]. However, only 2 articles have reported male sex as a potential risk factor for POD in patients undergoing head and neck reconstructive surgery [8, 11]. In the univariate analyses of most individual studies on POD after head and neck reconstructive surgery, male sex was not identified as a significant risk factor for developing POD (5 articles) [9, 10, 12-14]. Similarly, in other surgical areas, the results of meta-analyses of these patient groups were heterogeneous [20, 21]. These discrepancies between studies might suggest a higher incidence of confounders among the risk factors present in the male population.

ASA physical status may also be a predictor of POD after head and neck surgery [18]. However, there was no association between ASA and POD in the present study. Similarly, none of the 3 retrospective studies that examined the association between the ASA level and POD in patients undergoing head and neck reconstructive surgery identified any significant differences [9, 11, 13].

An increased surgery duration is considered a precipitating factor of POD [7]. Although head and neck reconstructive surgery inevitably results in lengthy operative times, lengthy operative and anesthesia times were not identified as a significant risk factor for the development of POD in the univariate analysis of our study. Similarly, lengthy operative time was not identified as a significant risk factor for developing POD in the univariable analyses conducted by Makiguchi et al. and Ishibashi et al. [9, 11].

The present study also examined the association between two inflammatory biomarkers (CRP and NLR)

and POD. In the univariate analysis, neither CRP (preoperative, postoperative, and ΔCRP [preoperative CRP minus postoperative CRP]) nor NLR showed a significant association with the development of POD. Several meta-analyses have investigated the association between CRP and postoperative delirium [22, 23]. Higher preoperative CRP values may be associated with POD development in cardiac, orthopedic, and abdominal surgery. In contrast, no significant association between CRP and POD was identified in other types of surgery. The association between preoperative NLR and POD is controversial. In patients undergoing head and neck free-flap reconstruction, a higher preoperative NLR may be associated with the development of POD [13]. In contrast, Kato et al. [24] and Ida et al. [25] found no significant association between the preoperative NLR and POD.

Sedation with DEX after non-cardiac surgery decreases the incidence of POD [26]. A systematic review and meta-analysis [27] suggested that the intraoperative use of DEX could reduce the incidence of POD in surgical patients. In our study, sedation with DEX after surgery was not associated with a reduction in the incidence of POD. One possible explanation for this is that the cases sedated with DEX in the present study included patients whose DEX was sedated in combination with propofol, which may have affected the results. Postoperative delirium results from multifactorial etiologies, so it is challenging to predict and treat completely.

This study had several limitations. First, it was a single-center study with a small sample size and a retrospective observational research design. The low number of cases is because this study was limited to cases involving oral tumors and reconstructive surgery. In this study, almost all diagnoses of delirium were made by a psychiatrist. Although we did not mention the diagnostic criteria used, the diagnosis of delirium in all of our patients was based on documentation that corresponded to the diagnostic criteria stated in DSM-5. There was a high likelihood that we might have missed cases of hypoactive-type delirium in this study. We did not have a standardized protocol for psychiatric intervention. Therefore, preoperative responses and outcomes may have varied depending on the psychiatrist who performed the preoperative consultation. We did not evaluate the presence of preoperative cognitive impairment, which has been identified as a risk factor for POD. Finally, we did not assess the severity of delirium, evaluate the validity of pain control, or length of hospital stay. We hope to examine these aspects in future studies.

In conclusion, this study found no significant difference between the incidence of POD and perioperative factors. Additionally, preoperative psychiatric intervention did not reduce the incidence of POD. However, further prospective studies are needed.

Sources of support

No funds were received for this research.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yukie Nitta: Writing − original draft, Investigation, Data curation. **Takuro Sanuki**: Writing − review & editing, Investigation. **Shigekazu Sugino**: Investigation, Data curation. **Masahiro Sugimoto**: Investigation, Data curation. **Kanta Kido**: Writing − review & editing, Supervision, Conceptualization.

References

[1] Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc.; 2013.

[2] McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? J Am Geriatr Soc 2003;51(11):1539-46. doi: 10.1046/j.1532-5415.2003.51509.x

[3] Schubert M, Schürch R, Boettger S, Garcia Nuñez D, Schwarz U, Bettex D, et al. A hospital-wide evaluation of delirium prevalence and outcomes in acute care patients - a cohort study. BMC Health Serv Res 2018;18(1):550. doi: 10.1186/s12913-018-3345-x

[4] Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383(9920):911-22. doi: 10.1016/S0140-6736(13)60688-1

[5] Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth 2020;125(4):492-504. doi: 10.1016/j.bja.2020.06.063

[6] Krewulak KD, Stelfox HT, Leigh JP, Ely EW, Fiest KM. Incidence and Prevalence of Delirium Subtypes in an Adult ICU: A systematic review and meta-analysis. Crit Care Med 2018;46(12):2029-35. doi: 10.1097/CCM.0000000000003402

[7] Swarbrick CJ, Partridge JSL. Evidence-based strategies to reduce the incidence of postoperative delirium: a narrative review. Anaesthesia 2022;77 Suppl 1:92-101. doi: 10.1111/anae.15607

[8] Densky J, Eskander A, Kang S, Chan J, Tweel B, Sitapara J, et al. Risk factors associated with postoperative delirium in patients undergoing head and neck free flap reconstruction. JAMA Otolaryngol Head Neck Surg 2019;145(3):216-21. doi: 10.1001/jamaoto.2018.3820

[9] Makiguchi T, Yokoo S, Kurihara J. Risk factors for postoperative delirium in patients undergoing free flap reconstruction for oral cancer. Int J Oral Maxillofac Surg 2018;47(8):998-1002. doi: 10.1016/j.ijom.2018.03.011

[10] Choi NY, Kim EH, Baek CH, Sohn I, Yeon S, Chung MK. Development of a nomogram for predicting the probability of postoperative delirium in patients undergoing free flap reconstruction for head and neck cancer. Eur J Surg Oncol 2017;43(4):683-8. doi: 10.1016/j.ejso.2016.09.018

[11] Ishibashi-Kanno N, Takaoka S, Nagai H, Okubo-Sato M, Fukuzawa S, Uchida F, et al. Postoperative delirium after reconstructive surgery for oral tumor: a retrospective clinical study. Int J Oral Maxillofac Surg 2020;49(9):1143-8. doi: 10.1016/j.ijom.2020.01.018

[12] Taxis J, Spoerl S, Broszio A, Eichberger J, Grau E, Schuderer J, et al. Postoperative delirium after reconstructive surgery in the head and neck region. J Clin Med 2022;11(22). doi: 10.3390/jcm11226630

[13] Kinoshita H, Saito J, Takekawa D, Ohyama T, Kushikata T, Hirota K. Availability of preoperative neutrophil-lymphocyte ratio to predict postoperative delirium after head and neck free-flap reconstruction: A retrospective study. PLoS One 2021;16(7):e0254654. doi: 10.1371/journal.pone.0254654

[14] Takahashi N, Hiraki A, Kawahara K, Nagata M, Yoshida R, Matsuoka Y, et al. Postoperative delirium in patients undergoing tumor resection with reconstructive surgery for oral cancer. Mol Clin Oncol 2021;14(3):60. doi: 10.3892/mco.2021.2222

[15] Collinsworth AW, Priest EL, Campbell CR, Vasilevskis EE, Masica AL. A Review of multifaceted care approaches for the prevention and mitigation of delirium in intensive care units. J Intensive Care Med 2016;31(2):127-41. doi: 10.1177/0885066614553925

[16] Bui M, Thom RP, Hurwitz S, Levy-Carrick NC, O'Reilly M, Wilensky D, et al. Hospital length of stay with a proactive psychiatric consultation model in the medical intensive care unit: A prospective cohort analysis. Psychosomatics 2019;60(3):263-70. doi: 10.1016/j.psym.2018.07.011

[17] Angel C, Brooks K, Fourie J. Standardizing management of adults with delirium hospitalized on medical-surgical nits. Perm J 2016;20(4):16-002. doi: 10.7812/TPP/16-002

[18] Dong B, Yu D, Jiang L, Liu M, Li J. Incidence and risk factors for postoperative delirium after head and neck cancer surgery: an updated meta-analysis. BMC Neurol 2023;23(1):371. doi: 10.1186/s12883-023-03418-w

[19] Zhu Y, Wang G, Liu S, Zhou S, Lian Y, Zhang C, et al. Risk factors for postoperative delirium in patients undergoing major head and neck cancer surgery: a meta-analysis. Jpn J Clin Oncol

2017;47(6):505-11. doi: 10.1093/jjco/hyx029

[20] Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. Br J Surg 2016;103(2):e21-8. doi: 10.1002/bjs.10062

[21] Zhang HJ, Ma XH, Ye JB, Liu CZ, Zhou ZY. Systematic review and meta-analysis of risk factor for postoperative delirium following spinal surgery. J Orthop Surg Res 2020;15(1):509. doi: 10.1186/s13018-020-02035-4

[22] Noah AM, Almghairbi D, Evley R, Moppett IK. Preoperative inflammatory mediators and postoperative delirium: systematic review and meta-analysis. Br J Anaesth 2021;127(3):424-34. doi: 10.1016/j.bja.2021.04.033

[23] Adamis D, van Gool WA, Eikelenboom P. Consistent patterns in the inconsistent associations of Insulin-like growth factor 1 (IGF-1), C-Reactive Protein (C-RP) and Interleukin 6 (IL-6) levels with delirium in surgical populations. A systematic review and meta-analysis. Arch Gerontol Geriatr 2021;97:104518. doi: 10.1016/j.archger.2021.104518

[24] Kato K, Kinoshita H, Kumagai G, Takekawa D, Nitobe Y, Asari T, et al. Association between preoperative neutrophil-lymphocyte ratio, uric acid, and postoperative delirium in elderly patients undergoing degenerative spine surgery. J Anesth 2024;38(1):35-43. doi: 10.1007/s00540-023-03273-6

[25] Ida M, Takeshita Y, Kawaguchi M. Preoperative serum biomarkers in the prediction of postoperative delirium following abdominal surgery. Geriatr Gerontol Int 2020;20(12):1208-12. doi: 10.1111/ggi.14066

[26] Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388(10054):1893-902. doi: 10.1016/S0140-6736(16)30580-3

[27] Duan X, Coburn M, Rossaint R, Sanders RD, Waesberghe JV, Kowark A. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. Br J Anaesth 2018;121(2):384-97. doi:

10.1016/j.bja.2018.04.046

[28] Janssen TL, Steyerberg EW, Faes MC, Wijsman JH, Gobardhan PD, Ho GH, et al. Risk factors for postoperative delirium after elective major abdominal surgery in elderly patients: A cohort study. Int J Surg 2019;71:29-35. doi: 10.1016/j.ijsu.2019.09.011

[29] Choi KJ, Tan M, Jones K, Sheski D, Cho S, Garrick T, et al. The impact of rounds with a psychiatry team in the intensive care unit: A prospective observational pilot study evaluating the effects on delirium incidence and outcomes. J Psychiatr Res 2023;160:64-70. doi: 10.1016/j.jpsychires.2023.02.011

[30] Rymaszewska J, Kiejna A, Hadryś T. Depression and anxiety in coronary artery bypass grafting patients. Eur Psychiatry 2003;18(4):155-60. doi: 10.1016/s0924-9338(03)00052-x

Figure Click here to access/download;Figure;Figure 1.docx

Figure 1.

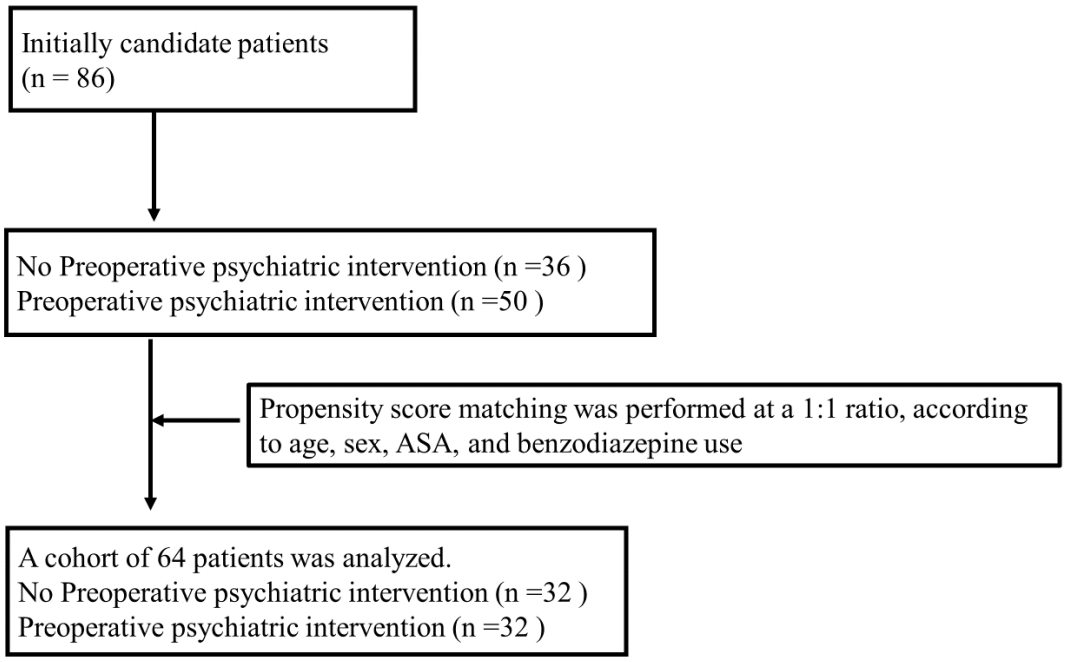

Table Click here to access/download;Table;Tables R2.docx

Table 1. Patients backgrounds

	Preoperative psychiatric intervention		p.value
	No intervention group (n=36)	Intervention group (n=50)	
Patient demographic characteristics			
Sex. Male (%)	23 (63.9)	31 (62.0)	1
Age (years)	65.0 [58.6, 73.3]	70.0 [57.3, 74.8]	0.335
BMI (kg/m^2)	22.2 [20.5, 25.1]	21.8 [19.4, 25.6]	0.789
Smoking history (%)	14 (38.9)	14 (28.0)	0.353
Alcohol consumption history n (%)*	18 (50.0)	18 (36.0)	0.268
BZD use (%)	1 (2.8)	15 (30.0)	0.001
ASA >=2 (%)	25 (69.4)	43 (86.0)	0.105
ACCI	8.0 [6.0, 9.0]	9.0 [7.3, 10.0]	0.078
Hypertension (%)	14 (38.9)	25 (50.0)	0.382
Diabetes mellitus (%)	8 (22.2)	13 (26.0)	0.801
Cerebrovascular disease (%)	1 (2.8)	7 (14.0)	0.131
Preoperative			
Serum albumin (g/dl)	4.1 [4.0, 4.3]	4.0 [3.6, 4.1]	0.017
Hemoglobin (mg/dl)	13.5 [12.4, 14.4]	12.8 [12.1, 13.8]	0.23
eGFR (mL/min/1.73m2)	72.6 [59.8, 88.8]	60.9 [53.5, 74.4]	0.008
CRP (IQR), g/dl	0.09 [0.04, 0.32]	0.07 [0.03, 0.54]	0.838
NLR	2.34 [1.57, 3.10]	2.68 [1.82, 3.73]	0.192
PLR	133.0 [115.2, 202.5]	155.4 [126.0, 191.1]	0.302
Malignant tumor (%)	29 (80.6)	45 (90.0)	0.227
Non-malignant (%)	7 (19.4)	5 (10.0)	0.227
Preoperative intervention			
Pharmacological intervention		15	
Ramelteon		12	
Suvorexant		3	
Intraoperative			
Neck dissection (%)	29 (80.6)	45 (90.0)	0.227
Operative time (min)	897 [796, 1062]	884 [778, 945]	0.182
Anesthesia time (min)	1002 [912, 1156]	957 [8697, 1027]	0.036
Fentanyl (μg/kg/h)	1.7 [1.4, 2.6]	2.3 [1.9, 2.7]	0.022
Remifentanil (μg/kg/h)	11.94 [9.63, 14.64]	8.79 [6.60, 10.99]	0.001
Blood loss (ml)	370 [273, 713]	465 [291, 809]	0.64
Urine volume (ml)	2485 [1760, 3613]	1930 [1525, 2991]	0.07
Blood transfusion volume (ml)	560 [0, 840]	560 [0, 560]	0.924
Total balance (ml)	3555 [2885, 4301]	3655 [3093, 4691]	0.333
Glu (IQR), mg/dl	139 [124, 164]	138 [120, 159]	0.643
Lac (IQR)	1.9 [1.69, 2.8]	1.7 [1.3, 2.3]	0.152
ABPm=>55mmHg and =>15min (%)	5 (13.9)	7 (14.0)	1
Number of vasopressors >=3 (%)	8 (22.2)	5 (10.0)	0.138
Tempreture. max (℃)	38.3 [37.6, 38.8]	37.85 [37.4, 38.3]	0.082
Postoperative			
CRP on postoperative day 1 (mg/dl)	7.0 [5.1, 9.0]	6.4 [4.9, 7.3]	0.154
Poropofol use at ICU (%)	13 (36.1)	8 (16.0)	0.043
DEX use at ICU (%)	23 (63.9)	42 (84.0)	0.043

Data are presented as medians [25%, 75% interquartile ranges] or numbers (percentages)

Abbreviations: POD, postoperative delirium; BMI, body mass index; BZD, benzodiazepine; ASA, American Society of Anesthesiologists Physical Status; ACCI, age-adjusted Charlson Comorbidity Index; CRP, C-reactive protein; eGFR, estimated Glomerular Filtration Rate; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Glu, glucose; Lac, lactate; ABPm, mean arteria blood pressure; DEX, dexmedetomidine; ICU, intensive care unit.

* Alcohol consumption history: estimated weekly ethanol intake of >=200 ml

Table 2. Characteristics of 64 propensity score matching patients

	Preoperative psychiatric intervention		p.value
	No intervention group (n=32)	Intervention group (n=32)	
Patient demographic characteristics			
Sex. Male (%)	19 (59.4)	20 (62.5)	1
Age (years)	65.00 [59.00, 73.25]	67.00 [55.00, 74.25]	0.898
BMI (kg/m^2)	21.85 [20.48, 25.22]	21.80 [19.40, 25.25]	0.752
Smoking history (%)	11 (34.4)	8 (25.0)	0.585
Alcohol consumption history n (%)*	15 (46.9)	11 (34.4)	0.446
BZD use (%)	1 (3.1)	1 (3.1)	1
ASA >=2 (%)	25 (78.1)	25 (78.1)	1
ACCI	8.00 [6.00, 9.25]	8.50 [7.00, 10.00]	0.334
Hypertension (%)	14 (43.8)	13 (40.6)	1
Diabetes mellitus (%)	8 (25.0)	8 (25.0)	1
Cerebrovascular disease (%)	1 (3.1)	4 (12.5)	0.355
Preoperative			
Serum albumin (g/dl)	4.10 [4.00, 4.30]	4.00 [3.68, 4.12]	0.091
Hemoglobin (mg/dl)	13.45 [12.30, 14.25]	13.35 [12.28, 14.07]	0.804
eGFR (mL/min/1.73m^2)	70.90 [58.62, 88.80]	62.90 [56.10, 73.88]	0.087
CRP (IQR), g/dl	0.09 [0.04, 0.32]	0.04 [0.02, 0.21]	0.197
NLR	2.41 [1.57, 3.13]	2.27 [1.78, 3.55]	0.799
PLR	141.59 [115.18, 209.66]	155.41 [134.75, 184.58]	0.511
Malignant tumor (%)	25 (78.1)	28 (87.5)	0.509
Non-malignant (%)	7	4	0.509
Intraoperative			
Neck dissection (%)	25 (78.1)	28 (87.5)	0.509
Operative time (min)	882.50 [787.50, 1043.75]	884.00 [766.75, 946.00]	0.468
Anesthesia time (min)	995.00 [900.25, 1140.50]	961.00 [865.75, 1036.75]	0.153
Fentanyl (μg/kg)	31.93 [23.73, 41.65]	37.71 [29.22, 42.41]	0.243
Remifentanil (μg/kg)	207.01 [151.95, 248.11]	152.78 [118.33, 193.64]	0.016
Blood loss (ml)	370.00 [247.50, 618.75]	527.50 [313.75, 958.75]	0.049
Urine volume (ml)	2400.00 [1760.00, 3650.00]	1910.00 [1500.00, 3083.75]	0.103
Blood transfusion volume (ml)	560.00 [0.00, 560.00]	560.00 [0.00, 840.00]	0.532
Total balance (ml)	3507.50 [2823.75, 4130.00]	3655.00 [3190.50, 4827.75]	0.112
Glu (IQR), mg/dl	140.50 [122.50, 164.75]	140.00 [120.25, 159.50]	0.877
Lac (IQR)	1.85 [1.53, 2.73]	1.70 [1.28, 2.00]	0.148
ABPm=>55mmHg and =>15min (%)	4 (12.5)	3 (9.4)	1
Number of vasopressors >=3 (%)	7 (21.9)	3 (9.4)	0.302
Tempreture. max (℃)	38.20 [37.58, 38.73]	37.85 [37.48, 38.42]	0.439
Postoperative			
CRP on postoperative day 1 (mg/dl)	7.00 [5.04, 8.95]	6.41 [4.94, 7.26]	0.235
Propofol use at ICU (%)	13 (40.6)	7 (21.9)	0.177
DEX use at ICU (%)	19 (59.4)	25 (78.1)	0.177
POD (%)	7 (21.9)	9 (28.1)	0.774

Data are presented as medians [25%, 75% interquartile ranges] or numbers (percentages)

Abbreviations: POD, postoperative delirium; BMI, body mass index; BZD, benzodiazepine; ASA, American Society of Anesthesiologists Physical Status; ACCI, age-adjusted Charlson Comorbidity Index; CRP, C-reactive protein; eGFR, estimated Glomerular Filtration Rate; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Glu, glucose; Lac, lactate; ABPm, mean arteria blood pressure; DEX, dexmedetomidine; ICU, intensive care unit.

* Alcohol consumption history: estimated weekly ethanol intake of >=200 ml

Table3. Binary logistic regression analysis of postoperative delirium

Factor	**OR (95% CL)**	**p.value**
Preoperative psychiatric intervention	2.19 (0.60-7.99)	0.24
Remifentanil (μg/kg)	1.01 (1.00-1.01)	0.12
Blood loss (ml)	1.00 (1.00-1.00)	0.34

Abbreviations: OR, odds ratio: CI, confidence interval:

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *[Journal name]* and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Responses to the reviewer's comments

We appreciate the reviewers for their constructive and helpful suggestions. We have addressed each of the reviewer's comments point by point and believe that our manuscript has been significantly improved. We have ensured that all formatting and style requirements have been met.

In the revised manuscript, all changes made in response to the reviewers' comments are highlighted in RED

.

1. Study design (major concern):

The study design should address a primary question, yet the authors have set out two different objectives. Studying the incidence as a primary endpoint with a secondary evaluation of the chosen potential risk factors (preoperative, perioperative, and postoperative) is feasible. However, including a retrospective evaluation of preoperative psychiatric interventions on the incidence of POD is methodologically unsuitable, despite the authors finding no statistically significant difference.

Response: We agree with your suggestions and have significantly altered our study design. Instead of comparing the POD group and the no POD group, we will now be comparing the psychiatric intervention group with the no intervention group in the Introduction and Material and Methods sections, and with new analysis.

2. Purpose of the study (major concern):

The study of pre-operative psychiatric intervention on POD is the real originality of the article and should have been, in my opinion, the main focus of the study. The methodology used does not allow for subgroup analysis, such as whether preoperative psychiatric interventions reduce symptom intensity or hasten recovery.

Response:

We completely agree with your assertion that the strength of this study lies in its focus on pre-operative psychiatric intervention on POD. As a result, we have modified the primary objective, outcomes, and methods, including the statistical analysis, in the Introduction and Material and Methods sections.

2.1. Is it systematically performed by a senior?

Response:

The surgeons consulted the patients with the department of psychiatry; therefore, we did not know

precisely whether the psychiatrist was a senior.

2.2. While the authors wish to assess the value of a non-pharmacologic approach, it appears that the psychiatric intervention studied is essentially drug-related: it is necessary to specify the content of the pre-operative interview, or if it is merely a clinical and anamnestic assessment, the non-pharmacological measures associated with the treatment protocol prescribed by the psychiatrist (orientation stimuli, clear and repeated explanations, sleep support sleep quality, etc.). If the interventions vary among patients, the different types (cognitive and pharmacological, pharmacological alone) should be analyzed separately.

Response:

We acknowledge your concerns about the key points in this study. We have made the following changes in response to your feedback:

1. We have removed the "non-pharmacologic approach" from the manuscript.

2. Since there is no established explicit guideline or protocol for the prevention of POD, the assessment, treatment, and medication details, including drug regimen and doses, have depended on attending psychiatrists. According to electronic medical records in the hospital, psychiatrists explained what POD was to the preoperative patients, assessed the risk of POD, and shared this information with the surgeons and nurses. Patients diagnosed by the psychiatrists as high risk for POD were prescribed psychiatric medications at the psychiatrist's discretion preoperatively. We added the medication data in Table 1. The psychiatrist provided instructions to the attending oral surgeon on the medication regimen for the onset of POD. Additionally, the psychiatrist, at their discretion, provided postoperative follow-up commensurate with the patient's risk of POD and participated in the treatment of POD at the onset.

As you mentioned, we agree that obtaining detailed information and analyzing each factor, including psychiatric assessment and treatment protocol separately, is necessary. However, it was challenging to gather these details in this study due to the incomplete protocol. We are now planning a randomized controlled trial (RCT) study shortly.

We have also revised the description of the preoperative psychiatric intervention on Page 7, Lines 11-24.

2.3. If these measures are used, are they systematically implemented before or during the onset of POD?

Response:

There was no standard protocol for postoperative delirium (POD) treatment, so we were unable to provide a detailed explanation. In this retrospective study, "psychiatric intervention" essentially refers to whether the patients received consultations from psychiatrists as recommended by the surgeons. The specific intervention strategy was determined at the discretion of the psychiatrist. This is a limitation of our retrospective study.

2.4. There are few details about specific drug prescriptions for POD. I don't understand whether they are prescribed pre-operatively and given pre-operatively or post-operatively, after the onset of symptoms.

Response:

As per our review of the medical records, 30% (15 out of 50) of patients received specific drugs such as ramelteon or suvorexant before their surgery, following an assessment of their risk factors for postoperative delirium (POD). We have included this information in Table 1 under "preoperative intervention." However, we were unable to obtain detailed information regarding the specific choice of medication or the dosages from the records.

2.5. When prescribing medication, even if several different molecules were used, the dosages used should be specified and whether the prescription was effective for all the patients who had received a pre-operative prescription.

Response:

As previously mentioned, psychiatrists prescribed two drugs, either ramelteon or suvorexant, before the operation. Our analysis compared the pharmacological intervention group with the non-pharmacological intervention group in patients undergoing psychiatric intervention, and we found that there was no significant difference in the incidence of POD (33.3% vs. 32.9%). We have included this description in the Results section (Page 10, Line 7).

2.6. When the diagnosis is made by another specialist (such as a surgeon), is the management strictly identical (unspecified)?

Response:

If surgeons or nurses suspected postoperative delirium (POD) in patients who had not preoperatively received psychiatric consultation, they would consult the psychiatrists and follow their orders. We added this information on Page 7, Line 22.

2.7. Do patients at high risk of POD seem to have benefited from more intensive monitoring? In which way? Are they distributed over both groups in the identical way?

Response:

Surgeons and nurses paid more attention to patients diagnosed with a high risk of POD. However, special monitoring was not carried out in the ICU and ward; almost all patients received only standard monitoring. Please note that I have added this description on Page 7, Line 9.

3. Analysis of the risk factors (minor concern) :

The authors used the main risk factors identified in the literature for their study. However, in my opinion, some of them cannot be studied in this study, such as the use of dexmedetomidine post-operatively (in an intensive care unit), since there is no clear and systematic protocol described in their hospital (dexmedetomidine or other molecule or combined prescription). Consequently, concluding this potential protective factor against POD is challenging.

Response:

Thank you for your helpful suggestion. We agree that the study on postoperative delirium (POD) and the use of drugs was complex. As a result, we have revised the primary outcome from examining the risk factors of POD to assessing the impact of psychiatric intervention. We believe that your input has significantly strengthened this manuscript.

3.1. The risk factor 'number of teeth remaining pre-operatively' should be justified as an independent risk factor.

Response:

We want to investigate whether functions like biting or swallowing are associated with postoperative cognitive dysfunction (POD). Therefore, our focus is on the remaining teeth in the patients.

3.2. Risk factors that would have been of interest to study:

-the presence of malignancy (since the population under study is being treated for either cancer or osteoradionecrosis), especially since it is little studied as an independent risk factor in the literature concerning major head and neck surgery.

Response:

We appreciate your suggestion. In this study, since the number of non-cancer surgeries was low, we could not compare them with cancer and non-cancer including osteoradionecrosis.

-the surgical procedure, since the majority of head and neck cancer surgeries require unilateral or bilateral neck dissection, thus increasing operating time, blood loss and the number of drains, although the authors immediately mention this potential risk factor in their introduction. This is an important difference from patients operated on for osteoradionecrosis.

Response:

Relationship between cancer surgery and non-cancer surgery will be further explored as more data

becomes available in the near future. This revised manuscript emphasizes psychiatric intervention. We appreciate your important suggestion.

-the type of free flap used for reconstruction, as previously demonstrated by Kolk et al (2022).

Response:

We included the article you mentioned as Ref. 10. Initially, we were focusing on analyzing the risk factor of POD as the primary outcome, which would have involved examining the type of surgery procedure and other factors as Kolk et al. described. However, we have since shifted our main outcome to psychiatric intervention.

4. Study biases (minor concern):

4.1. Diagnostic criteria for POD: based on the DSM-V definition but should be better described or explained by the authors. Clarify how risk is assessed (some patients are described as high-risk). If necessary, make a figure to present the diagnostic criteria and their clinical evaluation.

Response:

We noted that on Page 14, Line 18, almost all cases of delirium were diagnosed by a psychiatrist. Consequently, we did not specify the diagnostic criteria employed, and the diagnosis of delirium in all our patients relied on documentation that aligned with the diagnostic criteria outlined in DSM-5. It's important to outline the risk of postoperative delirium (POD) in the upcoming randomized controlled trial (RCT) study.

4.2. It is also essential to specify whether all other differential diagnoses of postoperative confusion have been eliminated before the diagnosis of POD (confusion related to pain, to a perturbation in natremia, constipation, acute urinary retention, etc.). The authors report the bias related to the absence of data on the effectiveness of postoperative analgesia, but do not discuss other potential causes.

Response:

There are many causes of Postoperative Delirium (POD). When patients are suspected of having POD, physicians must first eliminate other complications, such as electrolyte imbalances or anemia, before diagnosing POD holistically. The presence of many contributing factors can make this diagnosis very challenging. Postoperative pain was one of the most significant factors for POD. Therefore, we discussed it in the Discussion section.

4.3. It would also be of interest to determine the reasons why not all patients had a pre-operative

psychiatric intervention (chronological considerations, psychiatrist availability, initial assessment by another caregiver who only calls the psychiatrist if there is a suspicion that the patient may be at risk of POD, etc.).

Response: In line with the information on Page 7, Line 15, it has been noted that national health insurance in Japan has included coverage for managing postoperative delirium in surgical patients since 2020. Prior to this, whether patients undergoing major head and neck surgery with reconstruction received preoperative psychiatric consultation depended on the surgeon's decision. However, post-2020, almost all patients underwent preoperative psychiatric consultations.

4.4. Potential confounding factors in the study:

-Post-operative sedation of patients for 12 hours (minimum?). The duration of anaesthesia is a debated issue in the current literature as an independent risk factor for the occurrence of POD. The use of sedative drugs should therefore be clearly specified. However, there is no mention of the duration of post-operative sedation in the ICU (it is simply stated that sedation is discontinued if the patient is still stable on Day 1, but it is not specified whether it has to be prolonged for some patients and for however long).

Response:

After their surgery, the majority of patients only stayed in the ICU for one day, typically from the night of the operation to the next morning (approximately 12 hours). In some instances, patients needed to stay in the ICU for up to two days because of respiratory issues. There were only a few cases, so it was hard to provide specific details.

5. Results

The results found by the authors on the incidence of POD and the assessment of associated risk factors are broadly consistent with the literature. While there are many articles on the occurrence of POD after major surgery, especially oncological procedures, there are comparatively few in the specific field of head and neck reconstruction surgery. Despite the relatively small size of the study, it confirms other findings in the literature on the multifactorial etiology of POD.

The occurrence of surgical complications should also be specified, specifically with regard to microsurgical anastomoses.

Response:

We agree with your opinion. We need to consider more detailed factors such as the surgical procedure, diagnosis, and whether the condition is cancerous or non-cancerous to analyze the risk factors for postoperative delirium (POD). However, we changed the main outcome to focus on psychiatric

intervention and POD, therefore we did not provide detailed information about that.

6. Modification of figures

6.1. Table 1: report the distribution of surgical indications for osteoradionecrosis and head and neck cancer.

Response: We added malignant tumor and non-malignant distribution to Table 1 and 2.

Add a figure to specify the diagnostic criteria for POD and their evaluation in clinical practice.

Response: Regrettably, we could not have the detailed diagnostic criteria for POD, because when postoperatively the surgeons or nurses strongly suspected the patient's POD from the symptoms such as disturbance of consciousness and a change in cognitive capacity, they consulted a psychiatric physician, who diagnosed whether that was POD, based on his experience. We could not understand the diagnosis process from the medical record.

7. Summary

Should better specify the specific context studied, that of major head and neck surgery.

Response: We appreciate your suggestion. We are currently planning a new randomized controlled trial (RCT) study on postoperative delirium (POD) in oral and maxillofacial surgery.

8. Conclusion

This article's originality lies in the evaluation of a pre-operative psychiatric intervention on the onset of POD in patients undergoing major head and neck surgery with free flap reconstruction. This study should have been designed with this goal in mind, with a retrospective study with the onset of POD in these patients as the primary endpoint. Because of the methodology used, this whole part of the study seems to me to be hard to publish as it stands, and in any case should not be promoted in this way.

The details of the preoperative psychiatric interventions, any associated non-pharmacological management protocols (e.g., orientation support), and drug prescriptions are described too vaguely and must be clarified. Additionally, the characteristics of the interventions and the distribution of etiologies in each group should be clearly defined.

This article should be published once the major and minor revisions have been addressed.

Response: We agree with your opinion and recognize the originality of this study in examining the evaluation of a pre-operative psychiatric intervention on the onset of POD in patients undergoing major

head and neck surgery with free flap reconstruction. As suggested, we have made considerable changes to the main purpose and analytical method to focus on the psychiatric intervention. However, we acknowledge that the details of the preoperative psychiatric interventions, non-pharmacological management protocols, and drug prescriptions need further clarification, as the intervention is still in an early stage and has not been established for any other surgeries. This study only indicates that the pre-operative psychiatric intervention was not effective for major head and neck surgery, signaling the need to explore more options and define the treatment for POD.

Again, we thank you for allowing us to strengthen our manuscript with your valuable comments and queries. We have worked hard to incorporate your feedback and hope that these revisions will advance our manuscript closer to publication in the *Journal of Stomatology, Oral and Maxillofacial Surgery*.

We look forward to hearing from you,

Sincerely yours,
Kanta Kido