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Prevalence of postoperative delirium with different combinations of intraoperative general anesthetic agents in patients undergoing cardiac surgery
A retrospective propensity-score-matched study

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Abstract

Postoperative delirium (PD) remains an issue in cardiac surgery despite the constant efforts to reduce its incidence. In this retrospective study, the incidence of PD was evaluated in patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) according to different primary anesthetic agents: sevoflurane and dexmedetomidine- versus propofol-based anesthesia.

A total of 534 patients who underwent heart-valve surgery or coronary artery bypass graft surgery with CPB between January 2012 and August 2017 were divided into 2 groups according to the main anesthetic agent: sevoflurane with dexmedetomidine (sevo-dex group, n = 340) and propofol (propofol group, n = 194). The incidence of PD was evaluated as the primary outcome. Patient-, surgery-, and anesthesia-related factors and postoperative complications were investigated as secondary outcomes. To reduce the risk of confounding effects between the 2 groups, 194 patients were selected from the sevo-dex group after propensity-score matching.

After propensity-score matching, the incidence of PD was not significantly different between the sevo-dex (6.2%) and propofol (10.8%) groups (P = .136). In comparisons of the incidence of each type of PD, only hyperactive PD occurred significantly less frequently in the sevo-dex group (P = .021). Older age, lower preoperative albumin levels, and emergency surgery were significant risk factors for PD.

The overall incidence of PD after cardiac surgery with CPB did not differ between patients receiving sevoflurane and dexmedetomidine-based versus propofol-based anesthesia. Only hyperactive PD occurred less frequently in patients receiving sevoflurane and dexmedetomidine-based anesthesia.

Abbreviations: ASA = American Society of Anesthesiologist, BMI = body mass index, CAM = confusion assessment method, CPB = cardiopulmonary bypass, ICU = intensive care unit, PD = postoperative delirium, RBC = red blood cell.

Keywords: cardiac surgery, dexmedetomidine, postoperative delirium, propofol, sevoflurane

1. Introduction

Delirium is associated with many adverse hospitalization outcomes, including increased mortality, nosocomial complications, poor 1-year functional recovery, and even postoperative cognitive decline.[1,2] Despite the constant efforts to reduce postoperative delirium (PD) by using various pharmacologic agents, reorientation, sleep protocols, early mobilization, nutrition,[3] it continues to be an issue in cardiac surgery patients.

Various risk factors for PD after cardiac surgery have been identified, including advanced age, preexisting cognitive impairment, cerebrovascular disease, metabolic syndrome, and the type and duration of surgery.[4,5] However, the effects of intraoperative anesthetic agents on PD in cardiac surgery remain underreported, unlike in non-cardiac surgery.[6] The occurrence of PD after cardiac surgeries was reported to be similar irrespective of the main anesthetic agents, inhalation agents, or propofol;[7,8] however, early postoperative cognitive dysfunction was less frequent in patients managed with inhalation anesthesia during cardiac surgery.[9,10]

Dexmedetomidine has been reported to be capable of reducing PD in cardiac[11–13] or non-cardiac surgery.[14,15] Accordingly, the potential addition PD-sparing effect of adding dexmedeto-

midine as an anesthetic adjuvant to general anesthesia for cardiac surgery has been hypothesized in previous studies.

In this retrospective study, we investigated the incidence of PD after cardiac surgery according to different combinations of intraoperative main anesthetic agents: sevoflurane with dexmedetomidine- versus propofol-based anesthesia.

2. Methods

2.1. Study population and data collection

After obtaining approval from the Institutional Review Board, electronic medical records from January 2012 to July 2017 were reviewed retrospectively. The requirement for informed consent was waived.

Adult patients aged 20 years or over who had undergone heart valve or coronary artery bypass graft surgery with cardiopulmonary bypass (CPB) were included in this retrospective study. Patients who had been preoperatively diagnosed with neuropsychological diseases such as dementia or Parkinson disease were excluded. Patients with visual disturbances, hearing loss, or reoperation due to postoperative complications were excluded as well. We also excluded patients who required postoperative sedation for any reason because PD might remain unnoticed due to sedation.

2.2. General anesthesia practice

Routine cardiac anesthesia of our institution from 2012 to 2017 could be divided into 2 categories according to the main intraoperative anesthetic agents; one group that received sevoflurane and dexmedetomidine (sevo-dex group) and the other group with propofol-based anesthesia (propofol group). The main differences related to the cardiac anesthesia practice were as follows.

In the sevo-dex group, anesthesia was induced with intravenous propofol, remifentanil, and sevoflurane. During the intraoperative period, anesthesia was maintained with sevoflurane and dexmedetomidine. Dexmedetomidine was administered continuously at 0.5 μg/kg/h during the entire anesthesia period. In the propofol group, total intravenous anesthesia was performed using propofol and remifentanil using a target-controlled infusion device (Orchestra; Fresenius vial, France). Dexmedetomidine was not used in the propofol group. The bispectral index was monitored to maintain a suitable anesthetic depth in all patients.

2.3. Assessment of postoperative delirium

PD was defined by positive results in assessments with the confusion assessment method for the intensive care unit (CAM-ICU) during the ICU stay. According to the standard ICU practice of our institution, direct bedside CAM-ICU assessments were performed and the results were recorded twice a day by well-trained nurses. After patients were transferred to the general ward, PD was assessed by nurses using the Nursing Delirium Screening scale in each nursing shift. The duration of delirium was defined as the total number of days for which the patients experienced PD in the ICU and general ward.

2.4. Other outcome variables

Data were collected and categorized into the following 3 variable sets: preoperative factors, including age, sex, weight, height, body mass index (BMI), American Society of Anesthesiologist (ASA) physical status classification, and preoperative laboratory findings; intraoperative factors, including the urgency of surgery, surgery time, CPB time, volume of estimated blood loss, and amount of red blood cell (RBC) transfusion; and postoperative factors, including duration of ICU stay, extubation time, postoperative admission period, postoperative complications, amount of RBC transfusion, and postoperative laboratory findings. Pre- and postoperative laboratory tests, including measurements of hematocrit values, platelet counts, and electrolyte, creatinine, and albumin levels, were performed within 1 month before surgery and within 24 hours after surgery, respectively. We investigated whether patients developed postoperative complications related to the renal and neurological systems.

2.5. Statistical analysis

Data are expressed as median (interquartile range) or number (proportion). All continuous data were assessed for normality by using the Shapiro-Wilk test. Incidence was analyzed using the chi-squared test or Fisher exact test. The Mann–Whitney U test or Wilcoxon signed-rank test was performed to compare the numerical data, as appropriate. A binary logistic regression model was used to evaluate the predisposing factors for PD. The dependent variable was the occurrence of PD and the independent variables were the main anesthetic drugs, age, sex, BMI, surgery type, ASA class, anesthesia time, CPB time, estimated blood loss, amount of RBCs transfused intraoperatively and postoperatively, and preoperative and postoperative hematocrit values and electrolyte, creatinine, and albumin levels.

Propensity-score matching was performed to reduce the risk of confounding effects between the sevo-dex and propofol groups.[16] Propensity scores were calculated using a logistic regression model. The covariate included sex, age, height, weight, BMI, ASA class, urgency of surgery, operation time, preoperative laboratory findings, estimated blood loss, duration of CPB, RBCs transfused intra- and postoperatively, extubation time, and type of surgery. The dependent variable was the main general anesthetic agent: inhalation with dexmedetomidine or propofol. We performed nearest-neighbor matching.[16] After propensity-score matching, the paired t test or Wilcoxon signed-rank test for continuous variables and the McNemar or McNemar-Bowker test for categorical variables were performed, as appropriate.

All analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corporation, NY). $P < .05$ was considered to indicate statistical significance.

3. Results

A total of 1283 patients were evaluated for eligibility, of whom 534 were finally analyzed. On the basis of the main general anesthetic agent, 340 and 194 patients were assigned to the sevo-dex and propofol groups, respectively. After propensity-score matching, 194 patients were selected from the sevo-dex group (Fig. 1).

The patient, surgery, and anesthesia characteristics were comparable between the 2 groups, except for the estimated blood loss volume, amount of RBCs transfused intra- and postoperatively, and the duration of ICU stay, which became comparable after propensity-score matching (Table 1).

The overall incidence, onset, and duration of PD were not significantly different between the sevo-dex and propofol
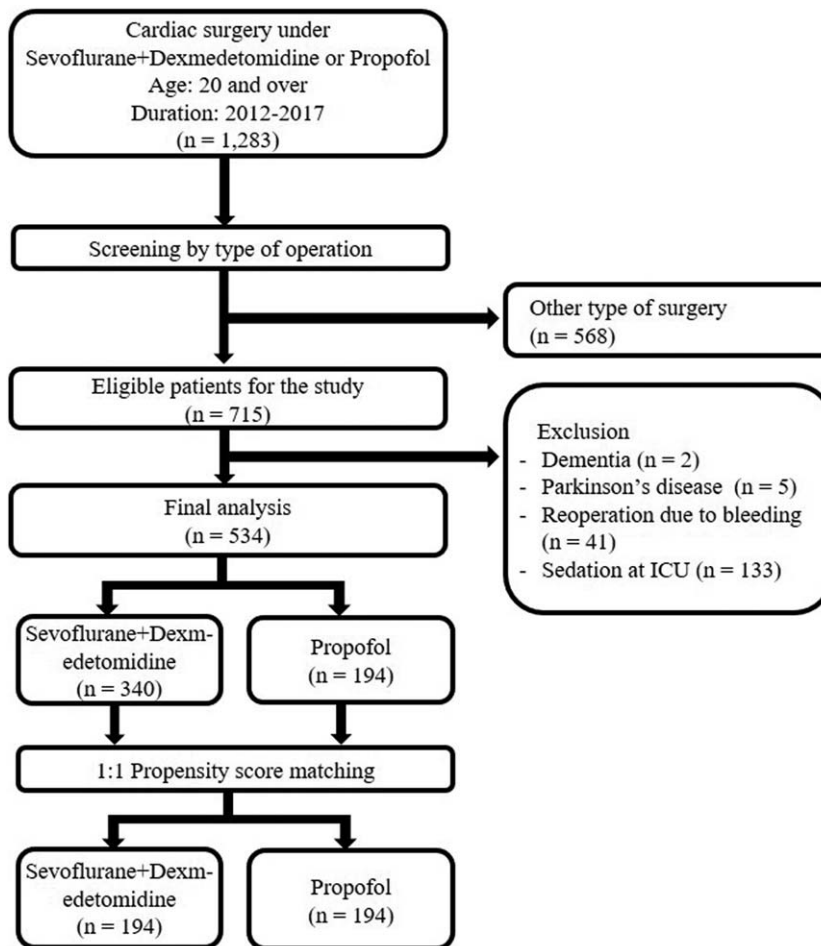
Figure 1. Flow diagram of patients' enrollment. ICU = intensive care unit.

Table 1

Characteristics of patients, surgery, and anesthesia.

	Before matching			After matching		
	Sevo-Dex (N = 340)	Propofol (N = 194)	P value	Sevo-Dex (N = 194)	Propofol (N = 194)	P value
Age, yr	70 (58–76)	68 (56–76)	.240	65 (56–74)	68 (56–76)	.483
Gender			.368			.845
Male	169 (50%)	105 (54%)		108 (56%)	105 (54%)	
Female	171 (50%)	89 (46%)		86 (44%)	89 (46%)	
Weight, kg	64 (57–71)	65 (58–71)	.445	66 (57–73)	65 (58–71)	.940
Height, cm	160 (153–168)	163 (155–169)	.053	162 (154–170)	163 (155–169)	.977
BMI, kg/m^2	25 (22–27)	24 (23–27)	.805	24 (23–27)	24 (23–27)	.781
ASA classification (1/2/3)			.318			.903
1	7	1		1	1	
2	64	38		43	38	
3	253	141		140	141	
4	16	14		10	14	
Surgery time, min	260 (216–305)	245 (215–300)	.364	255 (215–300)	245 (215–300)	.867
Anesthesia time, min	305 (265–355)	300 (265–345)	.398	300 (264–340)	300 (265–345)	.571
Estimated blood loss, mL	900 (600–1275)	800 (500–1000)	.002	800 (500–1000)	800 (500–1000)	.866
RBCs (mL, during surgery)	750 (400–1200)	600 (200–1000)	.008	500 (0–954)	600 (200–1000)	.354
RBCs (mL, after surgery)	0 (0–250)	0 (0–500)	<.001	0 (0–250)	0 (0–500)	.321
CPB, min	125 (93–155)	124 (98–146)	.344	123 (90–148)	124 (98–146)	.454
Elective/emergency	322 (95%)/18 (5%)	190 (98%)/4 (2%)	.075	189 (97%)/5 (3%)	190 (98%)/4 (2%)	1.000
Extubation, d	0 (0–1)	0 (0–1)	.286	0 (0–1)	0 (0–1)	.962
ICU stay, d	2 (1–2)	1 (1–2)	.024	1 (1–2)	1 (1–2)	.265
Postoperative hospital stay, d	9 (7–14)	9 (7–13)	.473	8 (7–12)	9 (7–13)	.331

Data are expressed as the median (interquartile range) or the number of the patients (proportion).
ASA = American Society of Anesthesiologist classification, BMI = body mass index, CPB = cardiopulmonary bypass, ICU = intensive care unit, RBC = red blood cell.

Table 2

Characteristics of postoperative delirium and complications.

	Before matching			After matching		
	Sevo-Dex (N = 340)	Propofol (N = 194)	P value	Sevo-Dex (N = 194)	Propofol (N = 194)	P value
PD (overall)	41 (12.1%)	21 (10.8%)	.779	12 (6%)	21 (10.8%)	.136
Hyperactive PD	26 (7.6%)	14 (7.2%)	1.000	4 (2.1%)	14 (7.2%)	.021
Hypoactive PD	12 (3.5%)	5 (2.6%)	.618	5 (2.6%)	5 (2.6%)	1.000
Mixed PD	3 (0.9%)	2 (1.0%)	1.000	3 (1.5%)	2 (1.0%)	1.000
Onset delirium (postoperative day)	0 (0–4)	0 (0–4)	.710	0 (0–4)	0 (0–4)	.194
Duration of delirium, d	0 (0–7)	0 (0–4)	.154	0 (0–7)	0 (0–4)	.153
Seizure	11 (3.2%)	2 (1.0%)	.148	7 (3.6%)	2 (1.0%)	.180
Acute kidney injury	2 (0.6%)	1 (0.5%)	1.000	1 (0.5%)	1 (0.5%)	1.000

Data are expressed as the median (interquartile range) or number of the patients (proportion).
PD = postoperative delirium.

groups, even after propensity-score matching (Table 2). Incidences of other postoperative complications (seizure and acute kidney injury) were comparable between the 2 groups (Table 2).

Preoperative hematocrit, sodium, potassium, creatinine, and albumin levels were comparable between the 2 groups. However, in the propofol group, lower hematocrit and potassium, and higher albumin levels were observed postoperatively compared with the sevo-dex group. These different laboratory findings became comparable after propensity-score matching (Table 3).

The following parameters were confirmed as significant determinants for the occurrence of PD by binary logistic regression analysis (Table 4): patients were 1.06 (95% CI: 1.03–1.10) times more likely to experience PD for every 1-year increase in age; patients who underwent emergency surgery were 5.76 (95% CI: 1.66–19.98) times more likely to experience PD than those who underwent elective surgery; and patients were 0.46 (95% CI: 0.22–0.98) times less likely to experience PD for every 1g/dL increase in preoperative albumin value.

4. Discussion

This study showed that the overall incidence of PD in cardiac surgery with CPB was not affected by the different combinations of intraoperative anesthetic agents (sevoflurane with dexmedetomidine vs propofol). Older age, emergency surgery, and lower preoperative albumin levels were factors contributing to PD occurrence in this study.

A recent meta-analysis reported no significant difference in the incidence of PD or postoperative cognitive impairment between inhalation anesthetics and propofol after coronary artery bypass graft surgery.[8] In non-cardiac surgery, similar results were reported via a systematic review and meta-analysis, which showed no evidence of a difference in the incidences of PD according to the type of anesthetic maintenance agents (inhalation vs propofol).[6]

The role of dexmedetomidine in reducing PD has been investigated. Duan et al[17] reported that perioperative dexmedetomidine could reduce PD in the entire adult population undergoing cardiac or non-cardiac surgery. In particular, postoperative sedation with dexmedetomidine was proven to

Table 3

Preoperative and postoperative laboratory results.

	Before matching					
	Sevo-Dex (N = 340)		Propofol (N = 194)			
	Preoperative	Postoperative	Preoperative	Postoperative	P₁	P₂
Hematocrit (%)	12.8 (11.2–14.2)	11.1 (10.1–12.1)	13.0 (11.5–14.3)	10.6 (9.5–12.0)	.269	.028
Sodium, mmol/L	139 (136–141)	139 (137–141)	139 (137–141)	139 (137–141)	.367	.171
Potassium, mmol/L	4.2 (3.9–4.4)	3.9 (3.6–4.2)	4.1 (3.9–4.4)	3.8 (3.4–4.1)	.438	.026
Creatinine, mg/dL	0.86 (0.70–1.05)	0.88 (0.74–1.09)	0.84 (0.66–0.99)	0.93 (0.77–1.15)	.117	.117
Albumin, g/dL	4.1 (3.6–4.4)	3.3 (3.0–3.7)	4.1 (3.8–4.4)	3.4 (3.1–3.7)	.336	.040
	After matching					
	Sevo-Dex (N = 194)		Propofol (N = 194)			
	Preoperative	Postoperative	Preoperative	Postoperative	P₁	P₂
Hematocrit (%)	13.1 (11.8–14.5)	10.9 (9.7–11.8)	13.0 (11.5–14.3)	10.6 (9.5–12.0)	.573	.692
Sodium, mmol/L	139 (137–141)	139 (137–141)	139 (137–141)	139 (137–141)	.598	.982
Potassium, mmol/L	4.2 (3.9–4.4)	3.8 (3.5–4.1)	4.1 (3.9–4.4)	3.8 (3.4–4.1)	.894	.899
Creatinine, mg/dL	0.84 (0.70–0.99)	0.88 (0.76–1.07)	0.84 (0.66–0.99)	0.93 (0.77–1.15)	.776	.093
Albumin, g/dL	4.2 (3.8–4.5)	3.4 (3.1–3.8)	4.1 (3.8–4.4)	3.4 (3.1–3.7)	.383	.645

Data are expressed as the median (interquartile range).
P_1 = compared the preoperative values between the 2 groups, P_2 = compared the postoperative values between the 2 groups.

Table 4

Binary logistic regression for the occurrence of postoperative delirium.

Independent variables	OR (95% CI)	*P*
Drug for anesthesia		.340
Propofol	1	
Sevoflurane+dexmedetomidine	0.71 (0.35–1.44)	
Age, yr	1.06 (1.03–1.10)	<.001
Gender		.839
Male	1	
Female	1.11 (0.40–3.12)	
BMI, kg/m^2	0.83 (0.59–1.18)	.295
Elective/emergency		.006
Elective	1	
Emergency	5.76 (1.66–19.98)	
ASA		.673
1	0.26 (0.02–4.08)	.341
2	0.17 (0.01–2.42)	.190
3	0.19 (0.01–3.18)	.247
4	0.00	1.000
Anesthesia time, min	1.01 (0.99–1.02)	.081
CPB time, min	1.01 (0.99–1.02)	.145
Estimated blood loss, mL	1.00 (1.00–1.00)	.521
RBCs (mL, during surgery)	1.00 (1.00–1.00)	.154
RBCs (mL, after surgery)	1.00 (1.00–1.00)	.076
Preoperative laboratory findings		
Hematocrit (%)	1.12 (0.90–1.39)	.314
Sodium, mmol/L	0.99 (0.89–1.10)	.827
Potassium, mmol/L	0.89 (0.42–1.90)	.761
Creatinine, mg/dL	1.78 (0.82–3.97)	.146
Albumin, g/dL	0.46 (0.22–0.98)	.043
Postoperative laboratory findings		
Hematocrit (%)	0.94 (0.76–1.17)	.604
Sodium, mmol/L	0.90 (0.79–1.03)	.123
Potassium, mmol/L	0.84 (0.39–1.78)	.644
Creatinine, mg/dL	0.53 (0.20–1.40)	.199
Albumin, g/dL	0.96 (0.48–1.93)	.910

ASA = American Society of Anesthesiologist, BMI = body mass index, CI = confidence interval, CPB = cardiopulmonary bypass, OR = odds ratio.

be effective for reducing PD in cardiac[11–13] or non-cardiac surgery[15,17] in comparison with midazolam or propofol.

However, the effect of intraoperative dexmedetomidine as an anesthetic adjuvant on PD has been a topic of debate.[17] Intraoperative dexmedetomidine seems to have a PD-sparing effect,[18,19] while several report showed no significant effect of dexmedetomidine in reducing the PD incidence.[20,21] In the present study, dexmedetomidine was administered only as an adjuvant to the inhalation anesthetic agent, and it showed no additional significant effect on PD reduction in comparison with propofol-based anesthesia.

Dexmedetomidine has been known to have neuroprotective effects.[22] However, the exact mechanism by which dexmedetomidine reduces the incidence of PD remains poorly understood. At present, the suggested delirium-sparing mechanisms based on the pharmacological characteristics of dexmedetomidine are as follows:[22–24] suppression of sustained increase of ⊠5 ɣ-aminobutyric acid type A receptor expression by anesthesia, maintenance of the anticholinergic level, and minimization of multiple neurotransmitter pathway disruptions. In a previous study performed in elderly patients who had undergone orthopedic surgery under regional anesthesia,[25] postoperative agitated behavior decreased more after intraoperative dexmedetomidine

sedation compared with propofol sedation. Unfortunately, the PD subtype could not be evaluated precisely in this study; therefore, more studies are needed to determine whether dexmedetomidine can be a potential preventive medication against the hyperactive PD type.

Risk factors for PD after cardiac surgery include advanced age, dementia, electrolyte derangement, prolonged CPB time, high perioperative transfusion requirement, low preoperative albumin level, high postoperative C-reactive protein concentration, and longer ICU stay.[26,27] Similar contributing factors were found in the present study, which included older age, emergency surgery, and lower preoperative albumin levels. In the present study, all included patients were adults, not elderly. Because increased age is a risk factor for PD in cardiac surgery, it is necessary to confirm whether different results can be drawn when only elderly patients are enrolled.

Before propensity-score matching, PD occurred in 12.1% of the patients in the sevo-dex group and 10.8% of those in the propofol group. After propensity-score matching, the incidence of PD in the sevo-dex group decreased remarkably from 12.1% to 6%, which can be attributed to the following factors. First of all, propensity-score matching reduced the mean age, which has been proven to be a risk factor for PD occurrence in the sevo-dex group. Moreover, estimated blood loss, perioperative transfusion requirement, and ICU stay were corrected by propensity-score matching. Thus, the severity of the patients' condition might have been corrected; therefore, the incidence of PD in the sevo-dex group appeared to have been adjusted. Even though the incidence of PD in the sevo-dex group decreased after propensity-score matching, there was no statistical difference in the incidence of PD between the 2 groups.

The present study had several limitations. First, due to the retrospective nature of this study, the anesthesia protocol was not randomized, and the basal anesthetic agents were different, that is, either sevoflurane or propofol. However, this study had its own implications since it proved that a combination of sevoflurane and dexmedetomidine did not offer superior PD reduction in comparison with propofol anesthesia. Second, our sample size was insufficient to achieve statistical significance in the incidence of PD between the 2 groups. Based on a post-hoc power analysis, this study had 6.3% power with a type 1 error of 5% to detect a decreased incidence of postoperative delirium in the sevo-dex group. The power increased from 6.3% to 39.9% after propensity score matching. However, the small cohorts in each group may not have been sufficient to ensure generalizability of results. To obtain statistical significance, >563 patients are required to ensure 80% power and a type I error of 0.05. Third, PD was evaluated by well-trained nurses using the CAM-ICU and the Nursing Delirium Screening scale. Because the purely hypoactive form of PD is usually more difficult to detect than the hyperactive form, the hypoactive form of PD might have been missed. Finally, this study was performed using data from a single center; therefore, its generalizability may be compromised.

In conclusion, the overall incidence of PD after cardiac surgery with CPB is not associated with the main anesthetic agent, that is, sevoflurane and dexmedetomidine-based versus propofol-based anesthesia. Further large randomized controlled trials are required to confirm the influence of the anesthetic on delirium.

Author contributions

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Formal analysis: Hyun-Jung Shin.
Methodology: Soo Lyoen Choi.
Supervision: Hyo-Seok Na.
Writing – original draft: Hyun-Jung Shin.
Writing – review & editing: Hyo-Seok Na.

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