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Association of Perioperative Dexmedetomidine Exposure with Flap Failure After Head and Neck Surgery Flap Reconstruction: A Retrospective Study

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Purpose: This study examined the relationship between perioperative dexmedetomidine exposure and postoperative flap outcomes following head and neck reconstruction.

Methods: This cohort study used the TriNetX Research Network to identify adults who underwent head and neck flap reconstruction for malignancy between 2014 and 2024. Perioperative dexmedetomidine exposure and outcomes were ascertained using medication records and Current Procedural Terminology (CPT) codes. Following matching, 2,522 patients per group were analyzed. The primary outcome was flap failure within 30 days of surgery. Secondary outcomes included 30-day blood vessel repair procedures, other flap revisions, mortality, acute kidney injury, and sepsis. Analyses at 14 and 90 days were exploratory.

Results: For the primary outcome, the dexmedetomidine group demonstrated lower flap failure rates compared with controls at 30 days (2.6% versus 4.1%; odds ratio [OR] 0.62, 95% confidence interval [CI] 0.45–0.85). Among secondary outcomes, a similar association was observed for blood vessel repair procedures (5.4% vs 7.7%; OR 0.69, 95% CI 0.55–0.87). No significant differences were observed in other outcomes. Exploratory temporal analyses revealed directionally consistent associations at 14 days (flap failure OR 0.54, 95% CI 0.37–0.79) and 90 days (flap failure OR 0.66, 95% CI 0.50–0.87). Sensitivity analyses excluding perioperative blood transfusion recipients and restricting the study to tertiary centers demonstrated directional consistency with the primary findings. Multivariable regression identified dexmedetomidine as independently associated with reduced flap failure (hazard ratio 0.60, 95% CI 0.46–0.78).

Conclusion: Perioperative dexmedetomidine exposure is associated with reduced flap failure and blood vessel repair, supporting the need for prospective randomized trials.

Keywords: dexmedetomidine, head and neck surgery, flap failure, free flap reconstruction

Introduction

Head and neck cancer ranks as the seventh most prevalent cancer globally, accounting for approximately 890,000 new diagnoses and 450,000 deaths each year.[1–3] Its incidence continues to rise worldwide, especially among younger individuals, driven by risk factors such as tobacco and alcohol use, betel nut chewing, and infections with human papillomavirus (HPV) or Epstein–Barr virus (EBV).[1–3] Head and neck free flap reconstruction represents a cornerstone technique for restoring form and function following oncologic resection in head and neck cancers; however, flap failure remains a notable complication, reported in approximately 4–8% of cases across large clinical series.[4–9] Multiple patient-related and surgical factors have been identified as contributors to the risk of flap failure, including diabetes mellitus, prolonged operative time, anemia, vasopressor use, alcoholism, and elevated preoperative platelet count.[9–14] Despite the clinical importance of flap survival and advances in

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surgical technique and postoperative monitoring,[8,15,16] large-scale clinical evidence evaluating modifiable perioperative pharmacologic factors that may influence flap outcomes remains limited.

Dexmedetomidine, a highly selective alpha-2 adrenergic agonist with sedative, analgesic, and anxiolytic properties, has gained widespread acceptance in perioperative and critical care settings.[17–19] Beyond its primary sedative effects, emerging evidence suggests that dexmedetomidine may exhibit additional properties, including anti-inflammatory effects, reduction of oxidative stress, and potential multi-organ protection.[19–23] Multiple studies across experimental and clinical settings have shown that dexmedetomidine enhances capillary perfusion, improves sublingual and renal microvascular flow, and alleviates ischemia/reperfusion-induced renal micro-circulatory dysfunction.[23–26] Collectively, these results support the hypothesis that dexmedetomidine confers microcirculatory and organ-protective benefits beyond sedation alone. However, comprehensive evidence specifically addressing the relationship between perioperative dexmedetomidine exposure and flap survival in patients undergoing head and neck reconstruction remains notably limited, and no large-scale studies have systematically evaluated this association in this unique high-risk population.

We hypothesized that perioperative dexmedetomidine administration might be associated with differences in flap failure rates after head and neck reconstruction surgery. Therefore, we conducted this large-scale retrospective cohort investigation using the TriNetX research network to examine the relationship between perioperative dexmedetomidine exposure and postoperative flap failure in patients undergoing head and neck free flap reconstruction. This study was designed as a hypothesis-generating observational analysis, and prospective randomized controlled trials will ultimately be required to confirm these associations and clarify their clinical implications.

Methods

Study Design and Data Source

This retrospective cohort investigation was conducted using data obtained from the TriNetX Research Network, a large-scale federated health research platform that integrates real-time, de-identified electronic health records from multiple healthcare organizations worldwide. The TriNetX system compiles comprehensive patient-level clinical information, including diagnostic data coded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and procedural information recorded using Current Procedural Terminology (CPT) codes. Through its standardized architecture and robust data-curation processes, the TriNetX platform ensures consistent data quality and has been extensively validated for use in epidemiological, surgical, and perioperative outcome studies.[27–29] The study protocol was reviewed and approved by the Institutional Review Board of the Chi Mei Medical Center (Approval No. 11406-E02). Given that the analysis relied exclusively on de-identified secondary data without direct patient contact, the requirement for individual informed consent was formally waived in accordance with institutional and ethical guidelines.

Study Population and Exposure Definition

We identified adult patients (≥18 years) diagnosed with malignant neoplasms of the larynx, accessory sinuses, nasal cavity, middle ear, lip, oral cavity, or pharynx who underwent flap reconstruction surgery between January 1, 2014, and December 31, 2024. Surgical procedures were ascertained using validated CPT codes for flap reconstruction, with the date of surgery designated as the index date. For patients with more than one eligible head and neck flap reconstruction during the study period, only the first surgical procedure was included, and subsequent surgeries were not considered in the analysis to ensure patient-level independence. Patients were stratified into two cohorts based on perioperative dexmedetomidine exposure: the dexmedetomidine group comprised patients who received dexmedetomidine on the surgical day, whereas the control group included those who did not.

Perioperative dexmedetomidine exposure was defined as documented administration on the day of surgery in the TriNetX database. Because medication records in this platform are date-based rather than phase-specific, this definition may encompass intraoperative use as well as early postoperative administration, including initiation in the post-anesthesia care unit or intensive care unit (ICU) on the same calendar day. Accordingly, exposure in this study should be interpreted as day-of-surgery perioperative exposure rather than being confined strictly to the intraoperative period.

This limitation is inherent to the structure of EHR-based medication data. To minimize misclassification related to postoperative ICU sedation, we excluded patients who received dexmedetomidine between postoperative days 1 and 30, thereby reducing the likelihood of capturing prolonged postoperative sedation rather than perioperative exposure.

Exclusion Criteria

To minimize confounding and ensure between-group comparability, we excluded patients with acute conditions within one month before surgery that could substantially influence postoperative outcomes. The exclusion criteria included sepsis (ICD-10: A41), ICU admission, respiratory failure (ICD-10: J96.X), acute kidney injury (ICD-10: N17.X), and coronavirus disease 2019 (ICD-10: U07.1). Additionally, we excluded patients with chronic kidney disease stages 4 and 5, end-stage renal disease, or those requiring hemodialysis, as these conditions could independently affect flap outcomes and perioperative management. Patients undergoing emergency surgery were excluded because their clinical context and decision-making processes fundamentally differ from those of elective procedures.

Propensity Score Matching

To approximate the conditions of a randomized controlled trial and address confounding inherent to observational research, we employed propensity score matching. Comprehensive baseline demographic data, comorbidities, and laboratory values were extracted from the TriNetX database for all eligible patients, covering a two-year period preceding the index surgery. A summary of all variables and corresponding ICD-10-CM codes used in the propensity score model is provided in Supplemental Table 1. However, detailed indicators of surgical complexity—such as operative duration, ischemia time, flap size, or intraoperative technical difficulty—were not available and therefore could not be incorporated into the matching model. Propensity scores representing the probability of receiving dexmedetomidine were calculated using multivariable logistic regression incorporating clinically relevant covariates, including age, sex, race, body mass index, comorbid conditions, and preoperative laboratory values. Patients were subsequently matched one-to-one using a greedy nearest-neighbor matching algorithm without replacement, applying a caliper width of 0.1 standard deviations of the logit of the propensity score. The adequacy of matching was rigorously assessed through standardized mean differences (with values <0.1 indicating satisfactory balance) and visual inspection of propensity score density distributions to confirm comparable baseline characteristics between cohorts.

Outcome Assessment

The prespecified primary outcome was the risk of flap failure, identified using validated CPT codes, occurring within 30 days postoperatively. Secondary outcomes at 30 days included the risks of blood vessel repair procedures, other flap revision procedures, all-cause mortality, acute kidney injury, and sepsis, all ascertained through validated ICD-10 and CPT codes in the TriNetX database. Flap-related outcomes were defined using procedure codes consistent with prior literature,[30] with specific CPT codes listed in Supplemental Table 2. ICU admission was evaluated as a marker of surgical complexity and illness severity, given that ICU admission is commonly scheduled for this patient population. Analyses at 14 and 90 days postoperatively were conducted as exploratory assessments to evaluate temporal patterns of associations, recognizing that multiple testing across time points may increase the likelihood of chance findings.

Follow-Up

Follow-up was defined based on the availability of subsequent healthcare encounters recorded within the TriNetX network after the index surgery. Outcomes were assessed at fixed postoperative time points of 14, 30, and 90 days. Because this is an EHR-based study, continuous follow-up cannot be ensured for all patients, and loss to follow-up may occur if patients seek care outside participating healthcare organizations. However, given that the study population underwent major surgical procedures and the outcomes of interest represent serious postoperative complications requiring hospital-based care, most clinically meaningful events within the short-term follow-up windows are likely to have been captured.

Sensitivity and Subgroup Analyses

To further evaluate the robustness and internal validity of our primary findings, we performed two complementary sensitivity analyses. Model I excluded patients who received perioperative blood transfusions within 14 days of surgery, thereby minimizing the potential influence of transfusion-related complications, such as immune reactions, hemodilution, or coagulopathy, which could confound the relationship between surgical exposure and outcomes. Model II limited the analysis to patients whose procedures were performed exclusively in tertiary medical centers, an approach intended to control for institutional-level variations in surgical expertise, perioperative care protocols, resource availability, and postoperative monitoring intensity.[31] In addition, a subgroup analysis was performed to explore potential effect modification by perioperative vasopressor exposure. Patients were stratified according to the use of agents, such as norepinephrine, dopamine, metaraminol, vasopressin, or phenylephrine, as previous studies have reported that vasopressor administration may influence microvascular perfusion and increase the risk of flap ischemia or failure.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics, with continuous variables presented as means with standard deviations and categorical variables as frequencies with percentages. Associations between dexmedetomidine exposure and outcomes were quantified using odds ratios (OR) with 95% confidence intervals (CI) derived from propensity-matched cohorts. Multivariable Cox proportional hazards regression models were constructed to adjust for clinically relevant covariates and identify independent predictors, with the results reported as hazard ratios (HR) and 95% confidence intervals. For propensity score–matched analyses, the TriNetX platform employs standard (unconditional) logistic regression and unstratified Cox proportional hazards models, rather than matched-pair approaches such as conditional logistic regression, stratified Cox models, or cluster-robust standard errors. For the Cox proportional hazards analysis, time zero was defined as the date of the index surgery. Patients were followed until the occurrence of flap failure or administratively censored at 30 days after surgery, whichever came first. Death without documented flap failure and loss of follow-up were treated as censoring events at the time of last recorded encounter. The proportional hazards assumption was assessed using Schoenfeld residual and was not violated ($p=0.218$).

Because flap failure was ascertained using CPT codes for revision procedures, precise event timing may be subject to measurement variability inherent to EHR-based data; therefore, ORs were designated as the primary effect estimates, with HRs from Cox models reported as supportive analyses. Separately, given the evaluation of multiple outcomes across several postoperative time points, the 30-day flap failure outcome was prespecified as the primary endpoint, whereas analyses at 14 and 90 days and other secondary outcomes were considered exploratory. No formal adjustment for multiple comparisons was applied; therefore, marginally significant findings should be interpreted with appropriate caution. Statistical significance was established at a two-sided alpha level of 0.05. All statistical analyses were performed using integrated analytical tools on the TriNetX platform, which does not permit explicit modeling of site-level random effects, clustering by healthcare organization, or detailed adjustment for temporal changes in practice patterns.

Results

Patient Selection and Baseline Characteristics

Using the TriNetX database, we initially identified 13,270 adult patients who underwent head and neck flap reconstruction for malignant neoplasms between January 2014 and December 31, 2024. Of these, 3,422 patients received perioperative dexmedetomidine and 9,848 did not. After applying clinical exclusion criteria, 1731 patients were excluded, resulting in 11,539 eligible patients (2,576 in the dexmedetomidine group and 8,963 in the control group). Among these eligible patients, 291 (2.5%) were further excluded due to missing data for key covariates required for propensity score matching, leaving 2,530 and 8,718 patients available for propensity score matching, respectively (Figure 1). Data availability for individual laboratory variables varied between groups: body mass index (82.8% vs 73.2%), hemoglobin (79.2% vs 74.0%), eGFR (77.2% vs 76.5%), albumin (53.9% vs 46.4%), HbA1c (22.9% vs 16.9%), and CRP (8.3% vs 6.7%) for the dexmedetomidine and control groups, respectively (Supplemental Table 3). Following 1:1 propensity score matching, 2,522 patients in each group were successfully matched with excellent covariate balance.

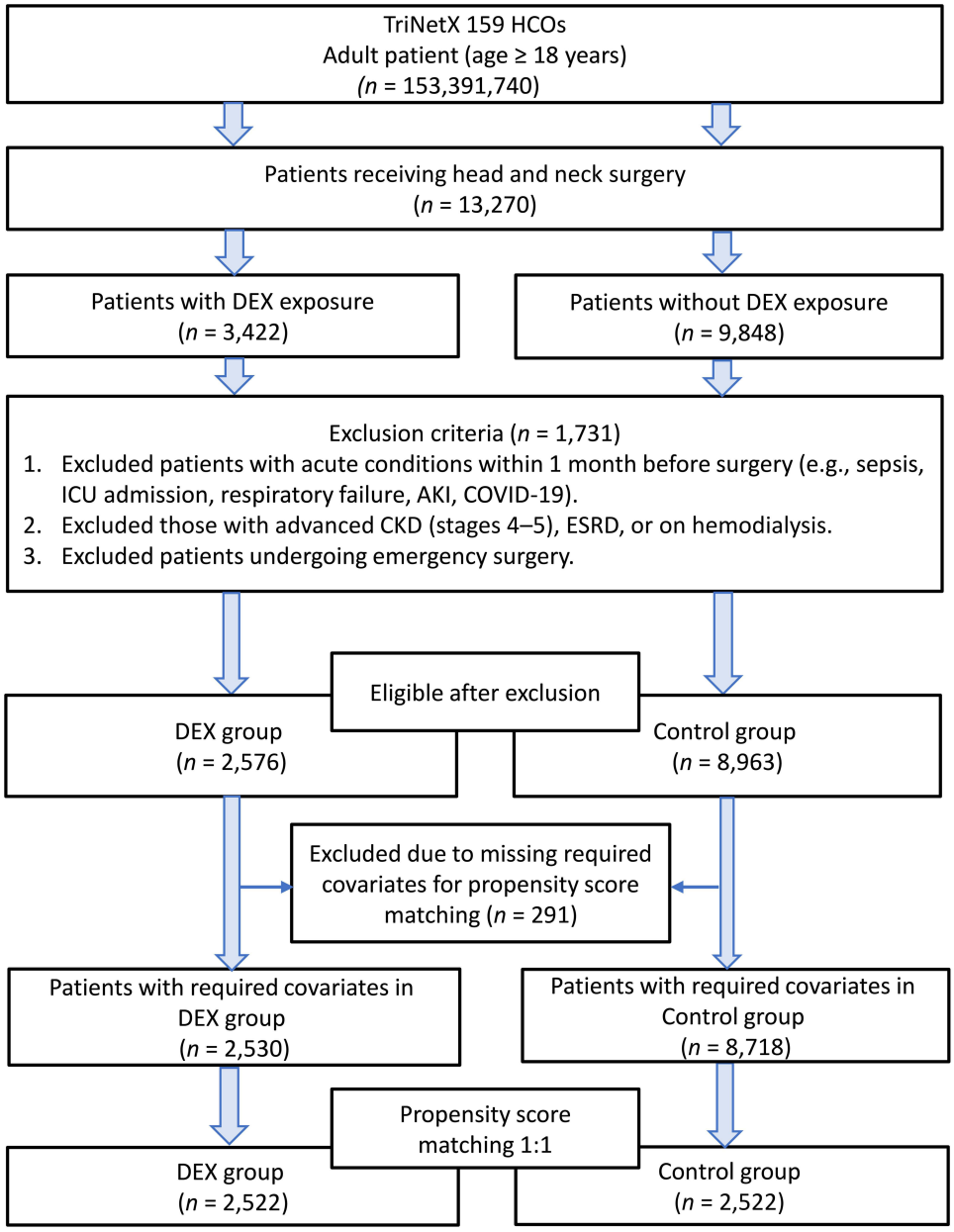

Figure 1 Patient selection flowchart from the TriNetX database.
Abbreviations: HCOs, Healthcare Organizations; CKD, chronic kidney disease; ESRD, End-Stage Renal Disease; AKI, acute kidney injury; ICU, intensive care unit; DEX, dexmedetomidine.

Before matching, several baseline differences existed between the groups. The DEX group showed a higher prevalence of essential hypertension (50.8% vs 42.7%), nicotine dependence (28.7% vs 22.2%), malnutrition (16.3% vs 10.8%), alcohol-related disorders (13.1% vs 6.7%), anemia (11.4% vs 7.8%), and liver disease (7.7% vs 5.2%) than the controls. After propensity score matching, all standardized mean differences were less than 0.1, indicating excellent balance across all measured covariates (Table 1). The matched cohorts demonstrated comparable distributions of age (62.4 vs 62.5 years), sex (32.4% vs 32.2% female), body mass index (26.3 vs 26.3 kg/m^2), racial composition, comorbidities, and laboratory values. Propensity score density distributions displayed substantial overlap after matching, confirming successful balancing between groups (Figure 2).

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Table 1 Baseline Characteristics of Patients Before and After Propensity Score Matching

Variables	Before Matching			After Matching		
	DEX Group (n = 2,530)	Control Group (n =8,718)	SMD†	DEX Group (n = 2,522)	Control Group (n = 2,522)	SMD†
Patient characteristics						
Age at index (years)	62.4±11.9	63.3±11.9	0.075	62.4±11.9	62.5±11.8	0.008
Female	817 (32.3)	2947 (33.8)	0.032	816 (32.4)	813 (32.2)	0.003
BMI kg/m^2	26.3±6.6	25.8±6.3	0.080	26.3±6.6	26.3±7.1	0.008
White	2057 (81.3)	6881 (78.9)	0.060	2050 (81.3)	2067 (82.0)	0.017
Black or African American	189 (7.5)	767 (8.8)	0.049	189 (7.5)	201 (8.0)	0.018
Unknown Race	100 (4.0)	420 (4.8)	0.042	99 (3.9)	82 (3.3)	0.036
Factors influencing health status and contact with health services	2158 (85.3)	7010 (80.4)	0.130	2150 (85.3)	2159 (85.6)	0.010
Comorbidities						
Essential (primary) hypertension	1285 (50.8)	3719 (42.7)	0.164	1277 (50.6)	1303 (51.7)	0.021
Nicotine dependence	725 (28.7)	1938 (22.2)	0.148	720 (28.5)	721 (28.6)	0.001
Ischemic heart diseases	424 (16.8)	1266 (14.5)	0.062	421 (16.7)	400 (15.9)	0.023
Malnutrition	412 (16.3)	941 (10.8)	0.161	405 (16.1)	411 (16.3)	0.006
Diabetes mellitus	406 (16.0)	1204 (13.8)	0.063	403 (16.0)	389 (15.4)	0.015
COPD	337 (13.3)	917 (10.5)	0.087	334 (13.2)	312 (12.4)	0.026
Alcohol related disorders	331 (13.1)	587 (6.7)	0.214	323 (12.8)	314 (12.5)	0.011
Overweight and obesity	299 (11.8)	665 (7.6)	0.142	295 (11.7)	321 (12.7)	0.031
Cerebrovascular diseases	284 (11.2)	775 (8.9)	0.078	283 (11.2)	263 (10.4)	0.026
Anemias	289 (11.4)	678 (7.8)	0.124	281 (11.1)	268 (10.6)	0.017
Diseases of liver	196 (7.7)	455 (5.2)	0.103	191 (7.6)	194 (7.7)	0.004
Chronic kidney disease	120 (4.7)	346 (4.0)	0.038	120 (4.8)	117 (4.6)	0.006
Antineoplastic chemotherapy	103 (4.1)	265 (3.0)	0.056	102 (4.0)	102 (4.0)	0.000
Vitamin D deficiency	101 (4.0)	270 (3.1)	0.048	99 (3.9)	89 (3.5)	0.021
Antineoplastic radiation therapy	96 (3.8)	196 (2.2)	0.090	94 (3.7)	79 (3.1)	0.033
COVID-19	41 (1.6)	78 (0.9)	0.065	39 (1.5)	32 (1.3)	0.024
Antineoplastic immunotherapy	26 (1.0)	61 (0.7)	0.035	26 (1.0)	27 (1.1)	0.004
Laboratory data						
Albumin g/dL (≥3.5 g/dL)	1267 (50.1)	3734 (42.8)	0.146	1261 (50.0)	1273 (50.5)	0.010
Hemoglobin≥12 g/dL	1738 (68.7)	5526 (63.4)	0.112	1731 (68.6)	1760 (69.8)	0.025
Hemoglobin A1c >7%	122 (4.8)	297 (3.4)	0.071	121 (4.8)	126 (5.0)	0.009
C-reactive Protein > 3 mg/L	175 (6.9)	454 (5.2)	0.072	173 (6.9)	167 (6.6)	0.009
eGFR >60 mL/min/1.73m^2	1824 (72.1)	5983 (68.6)	0.076	1816 (72.0)	1870 (74.1)	0.048

Notes: Data are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. †SMD values <0.1 indicate adequate balance between groups after matching.

Abbreviations: BMI, body mass index; SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

Association Between Dexmedetomidine Use and Postoperative Outcomes

At 30-day follow-up, the dexmedetomidine group demonstrated a lower incidence of flap failure compared to the control group (2.6% vs 4.1%; OR 0.62, 95% CI 0.45–0.85). Similarly, blood vessel repair procedures were less frequent in the dexmedetomidine group (5.4% vs 7.7%; OR 0.69, 95% CI 0.55–0.87). No meaningful differences were observed between groups for other flap revision procedures (OR 0.91, 95% CI 0.75–1.10), mortality (OR 0.80, 95% CI 0.49–1.31), acute kidney injury (OR 1.03, 95% CI 0.75–1.42), or sepsis (OR 0.95, 95% CI 0.65–1.38). ICU admission was more common in the dexmedetomidine group (OR 1.21, 95% CI 1.07–1.37) (Table 2).

For the 30-day analysis, the median follow-up time was 30 days (interquartile range, 0) in both the dexmedetomidine and control groups, with nearly identical mean follow-up durations. These metrics indicate comparable record activity

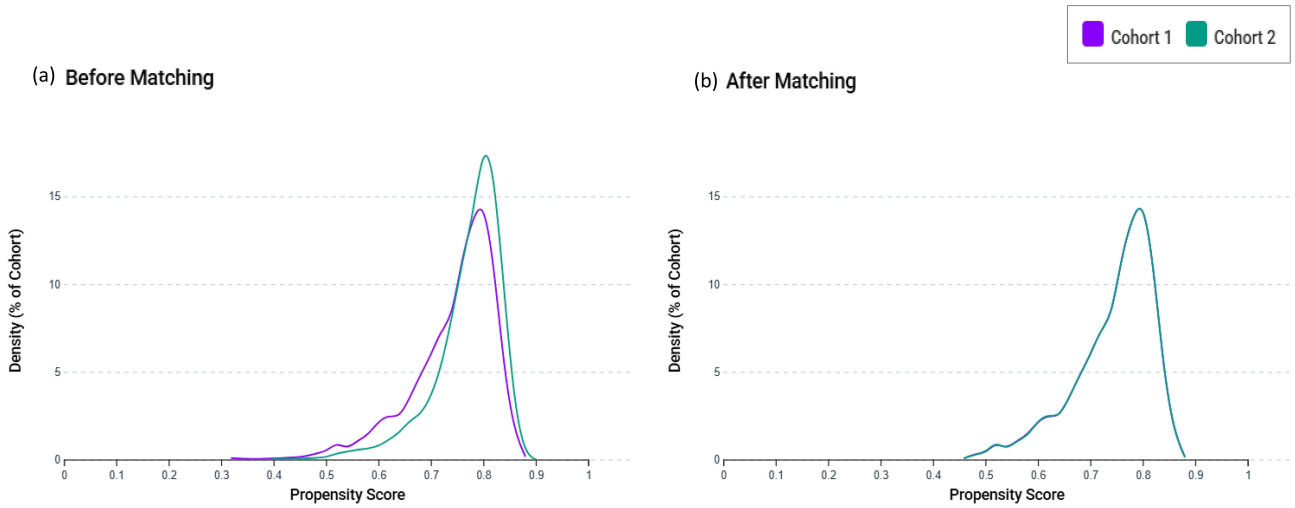

Figure 2 Propensity score distributions before and after matching. (**a**) Distribution of propensity scores between the dexmedetomidine (DEX) group (Cohort 1, purple) and the control group (Cohort 2, green) prior to matching, demonstrating an imbalance between cohorts. (**b**) Distribution of propensity scores after 1:1 propensity score matching by age at the index date, sex, race, laboratory data, and comorbidities, showing improved overlap and covariate balance between the two groups.

within the TriNetX network across groups during the prespecified follow-up window, although complete outcome capture cannot be guaranteed if care occurred outside contributing organizations.

Exploratory temporal analysis revealed consistent associations across the different follow-up periods (Table 3). At 14 days, dexmedetomidine use was associated with reduced flap failure (OR 0.54, 95% CI 0.37–0.79) and blood vessel repair (OR 0.71, 95% CI 0.56–0.90). At 90 days, these associations persisted for flap failure (OR 0.66, 95% CI 0.50–0.87) and blood vessel repair (OR 0.68, 95% CI 0.54–0.85), with a marginally significant reduction in other flap revision procedures (OR 0.85, 95% CI 0.72–1.00).

Sensitivity Analysis

Sensitivity analyses demonstrated directional consistency with the primary findings (Table 4). Model I, which excluded patients who received perioperative blood transfusions, demonstrated consistent associations between dexmedetomidine use and reduced flap failure (OR 0.59, 95% CI 0.42–0.83) and blood vessel repair (OR 0.70, 95% CI 0.54–0.89). Model II, restricted to 2,260 patients treated at tertiary medical centers, yielded similar results for flap failure (OR 0.62, 95% CI 0.44–0.87) and blood vessel repair (OR 0.70, 95% CI 0.55–0.88).

Table 2 Association Between Dexmedetomidine and 30-Day Postoperative Outcomes

Outcomes	DEX Group (n= 2,522)	Control Group (n= 2,522)	OR (95% CI)	P-value
	Events (%)	Events (%)		
Primary outcome				
Flap failure	65 (2.6%)	103 (4.1%)	0.62 (0.45–0.85)	0.003
Secondary outcome				
Blood vessel repair	137 (5.4%)	193 (7.7%)	0.69 (0.55–0.87)	0.001
Other flap revision procedures	226 (9.0%)	247 (9.8%)	0.91 (0.75–1.10)	0.310
Mortality	29 (1.2%)	36 (1.4%)	0.80 (0.49–1.31)	0.382
AKI	78 (3.1%)	76 (3.0%)	1.03 (0.75–1.42)	0.870
Sepsis	53 (2.1%)	56 (2.2%)	0.95 (0.65–1.38)	0.771
ICU admission	705 (28.0%)	612 (24.3%)	1.21 (1.07–1.37)	0.003

Notes: Data are presented as n (%) for event rates.
Abbreviations: DEX, dexmedetomidine; ICU, intensive care unit; AKI, acute kidney injury; OR, Odds ratio; CI, confidence interval.

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Table 3 Exploratory Temporal Analysis at 14-Day and 90-Day Follow-Up

Outcomes	2 weeks (n = 2,522)		90-day (n = 2,522)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Flap failure	0.54 (0.37–0.79)	0.001	0.66 (0.50–0.87)	0.003
Blood vessel repair	0.71 (0.56–0.90)	0.004	0.68 (0.54–0.85)	0.001
Other flap revision procedures	0.86 (0.68–1.10)	0.225	0.85 (0.72–1.00)	0.049
Mortality	0.60 (0.29–1.23)	0.156	0.93 (0.70–1.26)	0.651
AKI	1.37 (0.91–2.04)	0.128	0.92 (0.72–1.18)	0.521
Sepsis	1.00 (0.58–1.73)	1.000	0.99 (0.74–1.32)	0.941
ICU admission	1.25 (1.10–1.42)	0.001	1.20 (1.06–1.36)	0.004

Abbreviations: ICU, intensive care unit; AKI, acute kidney injury; OR, Odds ratio; CI, confidence interval.

Table 4 Exploratory Sensitivity Analyses at 30-Day Follow-Up

Outcomes	Model I		Model II	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Flap failure	0.59 (0.42–0.83)	0.002	0.62 (0.44–0.87)	0.005
Blood vessel repair	0.70 (0.54–0.89)	0.004	0.70 (0.55–0.88)	0.002
Other flap revision procedures	0.91 (0.74–1.12)	0.366	0.86 (0.70–1.05)	0.127
Mortality	1.00 (0.58–1.73)	1.000	0.72 (0.43–1.20)	0.201
AKI	1.10 (0.78–1.55)	0.599	1.08 (0.76–1.53)	0.658
Sepsis	1.36 (0.87–2.13)	0.176	1.00 (0.67–1.51)	1.000
ICU admission	1.17 (1.02–1.33)	0.026	1.13 (0.99–1.29)	0.070

Notes: Model I excluded patients receiving perioperative blood transfusions, yielding 2,233 matched pairs. Model II restricted analysis to tertiary medical centers, yielding 2,260 matched pairs.
Abbreviations: ICU, intensive care unit; AKI, acute kidney injury; OR, Odds ratio; CI, confidence interval.

Subgroup Analysis

Exploratory subgroup analysis stratified by perioperative vasopressor use revealed consistent associations across both strata (Table 5). Among the 1,686 patients receiving vasopressors, dexmedetomidine use was associated with reduced flap failure (OR 0.63, 95% CI 0.43–0.92) (Supplemental Table 4). Among the 830 patients without vasopressor use, a similar association was observed (OR 0.52, 95% CI 0.29–0.91) (Supplemental Table 5), with no significant subgroup difference detected (Table 5). The association between dexmedetomidine and reduced blood vessel repair procedures was significant in patients who did not use vasopressors (OR 0.60, 95% CI 0.41–0.88) and showed a borderline trend in those who received vasopressors (OR 0.76, 95% CI 0.57–1.00).

Table 5 Exploratory Subgroup Analysis Stratified by Vasopressor Use

Outcomes	Vasopressor Use (n = 1,686)		No Vasopressor Use (n = 830)		Subgroup Difference
	OR (95% CI)	P-value	OR (95% CI)	P-value	
Flap failure	0.63 (0.43–0.92)	0.015	0.52 (0.29–0.91)	0.020	0.585
Blood vessel repair	0.76 (0.57–1.00)	0.053	0.60 (0.41–0.88)	0.008	0.325
Other flap revision procedures	0.86 (0.68–1.08)	0.192	1.15 (0.81–1.61)	0.434	0.204
Mortality	0.87 (0.48–1.59)	0.645	NA	NA	NA
AKI	0.94 (0.64–1.39)	0.768	1.31 (0.73–2.37)	0.370	0.421
Sepsis	1.20 (0.77–1.88)	0.426	NA	NA	NA
ICU admission	1.06 (0.92–1.23)	0.391	1.15 (0.90–1.47)	0.263	0.587

Abbreviations: ICU, intensive care unit; AKI, acute kidney injury; OR, Odds ratio; CI, confidence interval; NA, not available due to insufficient numbers.

Table 6 Multivariable Predictors of 30-Day Flap Failure

Variable	Hazard Ratio (95% CI)	P-value
DEX vs control groups	0.60 (0.46–0.78)	<0.001
Male	0.98 (0.79–1.20)	0.807
Age at Index	0.99 (0.98–1.00)	0.032
Essential (primary) hypertension	1.11 (0.90–1.38)	0.334
Chronic kidney disease	0.42 (0.21–0.85)	0.016
Diabetes mellitus	0.99 (0.74–1.34)	0.967
Overweight and obesity	0.81 (0.56–1.19)	0.287
Nicotine dependence	0.82 (0.63–1.05)	0.110
Ischemic heart diseases	1.02 (0.77–1.36)	0.874
Alcohol-related disorders	1.45 (1.05–2.01)	0.023
Chronic obstructive pulmonary disease	1.30 (0.96–1.75)	0.086
Cerebrovascular diseases	1.17 (0.86–1.60)	0.314
Malnutrition	1.24 (0.94–1.64)	0.124
Diseases of liver	1.61 (1.15–2.24)	0.006

Notes: Hazard ratios with confidence intervals were derived from Cox regression models adjusting for relevant covariates in matched cohorts.
Abbreviations: DEX, dexmedetomidine; HR, hazard ratio; CI, confidence interval.

Multivariate Analysis to Identify Risk Factors for Postoperative Flap Failure

Multivariate Cox proportional hazards regression identified several independent predictors of 30-day flap failure (Table 6). Dexmedetomidine use was independently associated with a reduced risk (HR 0.60, 95% CI 0.46–0.78). Increasing age at surgery showed a marginal protective association (HR 0.99, 95% CI 0.98–1.00). Interestingly, chronic kidney disease was associated with a lower flap failure risk (HR 0.42, 95% CI 0.21–0.85). However, this finding was exploratory and should be interpreted with caution given the potential for selection bias, residual confounding, and chance. Conversely, alcohol-related disorders (HR 1.45, 95% CI 1.05–2.01) and liver diseases (HR 1.61, 95% CI 1.15–2.24) were independently associated with an increased risk of flap failure.

Discussion

In this large-scale retrospective cohort study, perioperative dexmedetomidine exposure was associated with reduced 30-day flap failure (the prespecified primary outcome) and blood vessel repair procedures (a secondary outcome) following head and neck free flap reconstruction. These associations remained directionally consistent across multiple sensitivity analyses, temporal windows, and multivariable adjustment. The consistency of these findings across different analytical approaches supports the observed associations, although the observational design precludes causal inference and the use of unconditional models after matching may result in underestimated uncertainty. Given the evaluation of multiple outcomes and time points without adjustment for multiple comparisons, findings beyond the primary endpoint should be considered hypothesis-generating.

Evidence regarding the relationship between dexmedetomidine and flap survival remains limited, consisting primarily of preclinical studies with sparse clinical data. Fang et al[32] demonstrated that high-dose dexmedetomidine in rat models is associated with improved random flap survival and reduced ischemia through mechanisms involving enhanced vascular endothelial growth factor expression, improved angiogenesis, and reduced oxidative stress and inflammatory markers. However, translating these experimental findings into clinical microvascular reconstruction remains uncertain. Clinical investigations in head and neck free flap surgery are scarce. Bista et al[33] conducted a small randomized trial of 20 patients comparing dexmedetomidine with fentanyl, finding that dexmedetomidine achieved optimal hemodynamic control and reduced blood loss without adverse effects on 7-day flap survival. Le et al[34] examined dexmedetomidine use upon emergence from anesthesia in 601 patients undergoing microvascular reconstruction and found associations with reduced postoperative neck hematoma formation and shorter hospital stays, though flap failure was not their primary

outcome. Despite these initial reports, comprehensive evidence systematically evaluating the relationship between perioperative dexmedetomidine exposure and flap survival across diverse populations remains lacking.

The present investigation identified a notable association between perioperative dexmedetomidine exposure and a reduced 30-day flap failure rate. This relationship demonstrated robustness across multiple analytical approaches designed to assess potential confounders. Exploratory time-dependent analyses provided additional insights into the durability of the observed associations. The association between dexmedetomidine exposure and lower flap failure rates was apparent as early as 14 days postoperatively, suggesting that any potential benefits may manifest during the critical early healing period when flaps are most vulnerable to ischemic complications. Importantly, this directional pattern persisted through 90 days of follow-up, indicating that the relationship extended beyond the immediate perioperative effects. This temporal consistency is noteworthy but does not represent independent confirmation, as systematic biases (eg, residual confounding or outcome misclassification) would be expected to persist across time points. Nonetheless, the consistent direction of effects across follow-up horizons provides modest supportive evidence, although time-specific estimates should be interpreted cautiously given the analytical limitations. The sustained nature of this association aligns with preclinical evidence,[32] suggesting that dexmedetomidine may influence fundamental tissue-level processes involved in wound healing and microvascular adaptation.

Subgroup analyses stratified by perioperative vasopressor exposure revealed that dexmedetomidine was associated with reduced flap failure, regardless of vasopressor administration. This finding aligns with recent evidence from Le et al,[34] who reported that vasopressor use was not significantly associated with increased flap failure or flap-related complications in head and neck reconstruction. Their analysis[34] demonstrated similar rates of flap failure, blood vessel repair, and other flap revision procedures between patients who did and did not receive vasopressors. The consistency between our subgroup findings and this independent investigation suggests that concerns about vasoactive medications compromising flap perfusion may be overstated. The absence of a significant subgroup difference in our analysis further suggests that the observed association between dexmedetomidine use and lower flap failure rates may operate through mechanisms that are independent of or complementary to traditional hemodynamic management approaches. However, this hypothesis warrants confirmation in future prospective and mechanistic studies.

The association between dexmedetomidine and reduced blood vessel repair procedures suggests a potential relationship with improved microvascular patency, as blood vessel repair typically reflects thrombotic events or technical complications affecting vascular anastomoses. However, no significant associations were identified between dexmedetomidine exposure and other flap revision procedures at 30 days, although a marginally significant association emerged at 90 days. Similarly, no significant relationships were observed between mortality, acute kidney injury, or sepsis within the study timeframe. The specificity of associations with flap failure and blood vessel repair, rather than broader surgical complications, suggests that the observed relationships may reflect effects more closely related to microvascular perfusion and flap viability rather than general perioperative outcomes.

The dexmedetomidine group demonstrated higher ICU admission rates compared with controls (28.0% vs 24.3%). However, ICU admission should be interpreted cautiously as it does not represent a direct outcome of dexmedetomidine exposure. ICU use in head and neck free flap reconstruction is protocol-driven and varies substantially by institution, time period, and case mix. This finding likely reflects unmeasured surgical complexity and institutional practice effects rather than any direct effect of dexmedetomidine. ICU admission serves primarily as a proxy for procedural complexity and institutional practice patterns, suggesting the dexmedetomidine group may have undergone more complex procedures or been treated at institutions with more liberal ICU protocols. Notably, despite this indicator of greater case complexity, the dexmedetomidine group exhibited lower rates of flap failure and blood vessel repair procedures. Nevertheless, residual confounding from unmeasured surgical and institutional factors remains possible, and the higher ICU admission rate underscores the limitations of observational comparisons in fully capturing case complexity and institutional practice variation.

Because outcomes were identified using CPT codes, it is not always possible to distinguish partial from total flap loss, and the categories of blood vessel repair and other flap revision procedures likely represent a spectrum of clinical scenarios, ranging from minor re-exploration to more extensive salvage operations. This heterogeneity may reduce the granularity of outcome classification and attenuate effect estimates through largely non-differential misclassification between exposure groups. Accordingly, the observed associations are best interpreted as reflecting overall patterns of

clinically meaningful flap-related interventions rather than precise estimates for specific types or severities of flap failure. In addition, the inverse association observed between chronic kidney disease and flap failure should be interpreted as exploratory rather than protective. This finding may reflect selection of lower-risk candidates for surgery, more cautious perioperative management, residual confounding from unmeasured factors, or a chance association.

A methodological consideration warrants discussion. The TriNetX platform employs standard (unconditional) logistic regression rather than matched-pair methods (eg, conditional logistic regression or generalized estimating equations with clustering by matched pair) for outcome comparisons in propensity score-matched cohorts. Austin[35] demonstrated that while paired and non-paired analytical approaches yield similar point estimates of treatment effects in propensity score-matched samples, non-paired methods may underestimate variance, potentially resulting in narrower confidence intervals and smaller p-values. Importantly, this limitation affects precision estimates rather than the direction or magnitude of the observed associations. Given these methodological considerations, our reported associations should be interpreted as reflecting consistent directional patterns rather than precise quantitative estimates, with the understanding that the true uncertainty surrounding these estimates may be greater than formally indicated.

This study has several limitations that warrant consideration when interpreting these findings. First, residual confounding cannot be excluded because several important determinants of flap outcomes—including flap type, flap size, primary versus secondary reconstruction, operative time and blood loss, surgeon and institutional experience, intraoperative technical difficulty, anesthetic technique, and intraoperative hemodynamic and fluid management—are not captured in the TriNetX database. Because outcomes were identified using CPT codes, it is not always possible to distinguish partial from total flap loss, and the categories of blood vessel repair and other flap revision procedures likely represent a spectrum of clinical scenarios, ranging from minor re-exploration to more extensive salvage operations. This heterogeneity may reduce the granularity of outcome classification and attenuate effect estimates through largely non-differential misclassification between exposure groups. Accordingly, the observed associations should be interpreted as hypothesis-generating rather than causal. Second, the database does not capture detailed information regarding dexmedetomidine dosing regimens, timing of administration, or duration of exposure, limiting our ability to assess dose-response relationships. Similarly, specific vasopressor agents, doses, and administration strategies were not differentiated in subgroup analyses. Because dexmedetomidine exposure was defined based on administration on the day of surgery, it is not possible to fully distinguish perioperative use from immediate postoperative ICU sedation in this EHR-based study, and the observed associations should not be interpreted as reflecting purely perioperative effects. Third, selection bias may exist if clinicians preferentially administer dexmedetomidine to certain patient populations based on unmeasured characteristics. The generalizability of the findings may be limited by the patient populations and practice patterns represented within the TriNetX network, which predominantly captures data from healthcare organizations in specific geographic regions. Additionally, long-term outcomes beyond 90 days, patient-reported outcomes, and functional assessments were not evaluated. Fourth, the study could not assess the specific mechanisms through which dexmedetomidine might relate to improved flap outcomes, as detailed physiological monitoring data were unavailable. Future studies incorporating objective measures of autonomic function and microvascular perfusion—assessment modalities that have been applied in other clinical contexts[36,37]—may help elucidate the mechanistic pathways underlying these associations. Fifth, the sensitivity analysis excluding patients who received perioperative blood transfusions should be interpreted cautiously, as conditioning on transfusion status—potentially influenced by both exposure and outcome—may introduce collider bias; thus, this analysis is exploratory rather than confirmatory. Finally, the multi-site, multi-year design of this observational study may have introduced unaccounted institutional and temporal effects that should be considered when interpreting the findings. Further, as follow-up in this EHR-based study relied on subsequent recorded encounters, loss to follow-up cannot be fully excluded, and differential follow-up between groups may have influenced fixed-time event estimates. Additionally, the TriNetX platform does not support matched-pair analytical methods for propensity score-matched comparisons; therefore, the reported confidence intervals may be narrower than those obtained using paired methods, and p-values should be interpreted with this consideration in mind. This complete-case approach may introduce selection bias if missingness was not completely at random. However, the direction of potential bias appears conservative: the dexmedetomidine group had higher data availability, suggesting inclusion of higher-acuity patients requiring more intensive monitoring, yet demonstrated lower flap failure rates.

Conclusion

In this large-scale retrospective cohort investigation utilizing propensity score matching, perioperative dexmedetomidine exposure was associated with reduced rates of 30-day flap failure (the prespecified primary outcome) and blood vessel repair procedures (a secondary outcome) following head and neck free flap reconstruction. These associations demonstrated directional consistency across multiple exploratory sensitivity analyses and temporal windows, though precision estimates should be interpreted with consideration of the analytical framework's limitations and the potential for chance findings given multiple testing. Although these observational findings cannot establish causality, they provide a rationale for prospective randomized controlled trials to determine whether perioperative dexmedetomidine administration directly improves flap survival in head and neck reconstruction.

Data Sharing Statement

Data for this study were obtained from the TriNetX Research Network under a collaborative agreement and are not publicly available. De-identified data may be accessed upon reasonable request from the corresponding author with TriNetX permission and subject to a data-sharing agreement or network membership.

Ethics Approval Statement

The study protocol was approved by the Institutional Review Board of Chi Mei Medical Center (IRB No. 11406-E02). The requirement for informed consent was waived in accordance with the institutional and regulatory guidelines for retrospective research.

Patient Consent Statement

Informed consent was not required because this retrospective study used de-identified preexisting data without any direct patient interaction.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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