Risk Factors for 30-Day Mortality After Head and Neck Microsurgical Reconstruction for Cancer: NSQIP Analysis

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Abstract

Objective. To identify the incidence and risk factors for 30-day postoperative mortality after microsurgical head and neck reconstruction following oncological resection.

Study Design. Retrospective case-control study.

Setting. American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database.

Methods. Microsurgical head and neck reconstructive cases were identified from 2005 to 2018 using Current Procedural Terminology codes and oncologic procedures using the International Classification of Disease 9 and 10 codes. The outcome of interest was 30-day mortality.

Results. The 30-day postoperative mortality rate was 1.2%. Univariate logistic regression analysis identified the following associations: age >80 years, hypertension, poor functional status, preoperative wound infection, renal insufficiency, malnutrition, anemia, and prolonged operating time. Multivariable logistic regression models were used to stratify further by the degree of malnutrition and anemia. Hematocrit <30% was found to be an independent risk factor for 30-day postoperative mortality (odds ratio [OR] = 9.59, confidence interval [CI] 2.32-39.65, P < .1) with albumin <3.5 g/dL. This association was even stronger with albumin <2.5 g/dL (OR = 11.64, CI 3.06-44.25, P < .01). One-third of patients (36.6%) had preoperative anemia, of which less than 1% required preoperative transfusion, although one-quarter (24.6%) required intraoperative or 72 hours postoperative transfusion.

Conclusions. Preoperative anemia is a risk factor for 30-day postoperative mortality. This association seems to get stronger with worsening anemia. Identification and optimization of such patients preoperatively may mitigate the incidence of 30-day postoperative mortality.

Keywords

head and neck cancer, microsurgical reconstruction, preoperative anemia, 30-day postoperative mortality

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Postoperative mortality after microsurgical head and neck cancer reconstruction is a devastating complication with varying incidences.¹⁴ Although late mortality in head and neck cancer patients can be attributed to cancer recurrence, early postoperative mortality is more closely related to the complications resulting from surgical resection and reconstruction.¹ The 30-day postoperative mortality after microsurgical head and neck cancer reconstruction has been reported to be less than 2%.²,³

Microsurgical reconstruction involves the transfer of skin, soft tissue, and sometimes bone from a remote donor site to the head and neck. With time, significant advancements have

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been made that have improved the safety and efficacy of these procedures.\textsuperscript{2,6} Historically, microsurgical flap survival has been considered the hallmark of success in head and neck reconstruction.\textsuperscript{7} Although technical and procedural factors hold primacy to the success of microsurgical reconstruction, patient-related risk factors mainly determine postoperative mortality.\textsuperscript{3} Because we often cannot “select” our patients with head and neck cancer, we can try to optimize them or attempt to mitigate risk factors.

The impact of demographics and comorbidities in determining perioperative mortality has not been studied using a large sample size. The American College of Surgeons’ National Surgical Quality Improvement Program (ACS NSQIP) is a multi-institutional database designed to improve the quality of care. The data in this database are collected prospectively and maintained from multiple institutions. The database is made available to the participating hospitals and comprises millions of patients with a multitude of variables. We sought to investigate the incidence and risk factors of 30-day postoperative mortality after microsurgical head and neck cancer reconstruction.

**Methods**

After obtaining Institutional Review Board approval from the University of New Mexico Health Science Center (IRB No. 20-092), the ACS NSQIP database participant data files from 2005 to 2018 were queried. The study was limited to a cohort of patients with head and neck cancer who underwent microsurgical reconstruction. The database was searched for free tissue transfer as the primary procedures using the following Current Procedural Terminology codes: muscle (15756), skin (15757), fascial (15758), and vascularized bone grafts (20955, 20956, and 20962). Head and neck cancer patients were identified using International Classification of Disease 9 and 10 codes, as shown in Supplemental Table S1.

Patient demographics included age, gender, and race. Medical comorbidities included obesity, diabetes, smoking, chronic obstructive pulmonary disease, hypertension requiring medication, bleeding disorders, preoperative steroid use, and functional dependence. Functional status is defined by the NSQIP as “the best physical functional status/level of self-care as demonstrated by the patient prior to the onset of acute illness.” Preoperative laboratory parameters included creatinine, albumin, hematocrit, white blood cell count, and platelet counts. The laboratory data were converted into categorical variables signifying risk factors, such as renal insufficiency for creatinine <1.2 g/dL, malnutrition for albumin <3.5 g/dL, anemia for hematocrit <36% for females and hematocrit <39% for males, and thrombocytopenia for a platelet count of <150,000/mm\(^3\). All laboratory data were obtained within 90 days of the index procedure. Operative characteristics included flap types, diagnosis by site, operating time, wound class, American Society of Anesthesiologists class, and procedure details such as lymph node dissection and tracheostomy, as shown in Table 1. In addition, intraoperative and 72-hour postoperative blood transfusion was used in the analysis.

Anemia was defined as a preoperative hematocrit of <36% for females and <39% for males within 30 days before the index operation.\textsuperscript{8,9} Anemia and malnutrition were further stratified to assess the correlation between their degree and severity of the outcome. Postoperative mortality was defined as any patient who died within the 30-day postoperative period. The following data were used dichotomously as risk factors for death: age ≥80 years, body mass index ≥30 kg/m\(^2\), and hematocrit <36% for females and <39% for males. The group comparison for categorical variables was performed using chi-squared and Fisher exact tests. The group comparison for continuous variables was performed using independent Student t test and nonparametric tests. Logistic regression models were generated to identify risk factors for 30-day postoperative mortality. The level of significance was set at \(\alpha = .05\). Missing data were not included in the analysis; no imputations were performed for this analysis. All statistical analysis was performed using SAS 9.4 (Cary, North Carolina).

**Results**

A total of 2356 patients were included in the analysis. This includes all flap types: muscle = 731 (31%), skin = 1131 (48%), fascial = 436 (18%), and vascularized bone = 58 (2.4%). Overall, 28 patients (1.2%) experienced mortality within the 30-day postoperative period. Using univariate logistic regression analysis, we identified associations between preoperative risk factors and 30-day post-operative period. Preoperative factors included advanced age (ie, age >80 years; odds ratio [OR] = 2.88, confidence interval [CI] 1.08-7.68, \(P = .03\)), poor functional status (OR = 5.94, CI 1.73-20.37, \(P < .01\)), hypertension requiring medication (OR = 2.32, CI 1.04-5.14, \(P = .04\)), preoperative wound infection (OR = 2.71, CI 1.02-7.21, \(P = .046\)), renal insufficiency (ie, creatinine <1.2 g/dL; OR = 3.24, CI 1.39-7.58, \(P < .01\)), malnutrition (ie, albumin <3.5 g/dL; OR = 4.54, CI 1.30-15.82, \(P = .02\)), anemia (ie, hematocrit <36 for females and hematocrit <39 for males; OR = 4.81, CI 2.01-11.49, \(P < .01\)), and prolonged operating time (ie, >9 hours; OR = 2.56, CI 1.15-5.68, \(P = .02\)), as shown in Table 2.

Multivariable logistic regression analysis was performed, adjusting for all of the associated preoperative risk factors. Four separate models were generated, and the area under the curve was generated to assess the test’s discrimination in predicting the outcome. We found that there was no independent risk factor when defining anemia with hematocrit <36% for females and hematocrit <39% for males. However, on further stratifying anemia by hematocrit <30% for both males and females, we found anemia to be an independent risk factor for 30-day postoperative mortality (OR = 9.59, CI 2.32-39.65, \(P < .01\)) with albumin <3.5 g/dL. This association was even stronger with albumin <2.5 g/dL (OR = 11.64 CI 3.06-44.25, \(P < .01\)), as shown in Table 3. The interaction term for anemia and malnutrition was not statistically significant, hence demonstrating no effect modification.

**Discussion**

This study aimed to evaluate 30-day postoperative mortality risk in patients undergoing microsurgical head and neck cancer reconstruction. Determining the incidence of mortality
### Table 1. Group Comparison.

|                      | Total, n (%) | Mortality, n (%) | No mortality, n (%) | P value |
|----------------------|--------------|------------------|---------------------|---------|
| **Age, y, median (IQR)** | 63, 55-72    | 71, 60-76        | 63, 55-71           | <.01    |
| **BMI, kg/m², mean ± SD** | 26.1 ± 6.4   | 25.6 ± 4.9       | 26.1 ± 6.4          | .67     |
| **Male**             | 1597 (67.8)  | 21 (75)          | 1576 (67.4)         | .41     |
| **White race**       | 1705 (88.5)  | 20 (87)          | 1685 (88.5)         | .74     |
| **Plastic surgery**  | 562 (24.3)   | 4 (15.4)         | 558 (24.4)          | .36     |
| **Diabetes**         | 330 (14.0)   | 6 (21.4)         | 324 (13.9)          | .26     |
| **Active smoking**   | 726 (30.8)   | 6 (21.4)         | 720 (30.9)          | .28     |
| **Dyspnea**          | 162 (6.9)    | 3 (10.7)         | 159 (6.8)           | .44     |
| **Functional status**| 49 (2.1)     | 3 (10.7)         | 46 (2)              | .02     |
| **Ventilator dependence** | 7 (0.3)       | 0 (0)             | 7 (0.3)             | >.99    |
| **History of COPD**  | 164 (7.0)    | 1 (3.6)          | 163 (7)             | .72     |
| **History of ascites** | 2 (0.1)     | 0 (0)             | 2 (0.1)             | >.99    |
| **History of CHF**   | 15 (0.6)     | 0 (0)             | 15 (0.6)            | >.99    |
| **Hypertension medication** | 1129 (47.9) | 19 (67.9)       | 1110 (47.7)         | .03     |
| **History of renal failure** | 1 (0.0) | 0 (0)             | 1 (0.0)             | >.99    |
| **Dialysis requirement** | 7 (0.3) | 0 (0)             | 7 (0.3)             | >.99    |
| **History of disseminated cancer** | 161 (6.8) | 3 (10.7) | 158 (6.8) | .43 |
| **Wound infection**  | 178 (7.6)    | 5 (17.9)         | 173 (7.4)           | .05     |
| **Chronic steroid use** | 99 (4.2)     | 2 (7.1)          | 97 (4.2)            | .33     |
| **Recent weight loss (>10% in 6 mo)** | 201 (8.5) | 3 (10.7) | 198 (8.5) | .72 |
| **Bleeding disorder** | 46 (2.0)     | 1 (3.6)          | 45 (1.9)            | .43     |
| **Blood transfusion in past 72 h** | 15 (0.6) | 0 (0)           | 15 (0.6)            | >.99    |
| **Chemotherapy in past 30 d** | 4 (0.2) | 0 (0)            | 4 (2.4)             | >.99    |
| **Radiotherapy in past 90 d** | 2 (0.1) | 0 (0)          | 2 (1.2)             | >.99    |
| **Presperis**        | 21 (0.9)     | 0 (0)            | 21 (0.9)            | >.99    |
| **Renal insufficiency** | 276 (12.9)   | 8 (32)           | 268 (12.7)          | <.01    |
| **Malnutrition**     | 206 (8.3)    | 5 (50)           | 201 (8.1)           | .02     |
| **Anemia**           | 730 (36.6)   | 19 (73.1)        | 711 (36.1)          | <.01    |
| **Thrombocytopenia** | 170 (7.9)    | 4 (14.8)         | 166 (7.8)           | .16     |
| **Wound class**      |              |                  |                     | .23     |
| 1, clean             | 547 (23.2)   | 7 (25)           | 540 (23.2)          |         |
| 2, clean/contaminated | 1699 (72.1)  | 18 (64.3)        | 1681 (72.2)         |         |
| 3, contaminated      | 75 (3.2)     | 2 (7.1)          | 73 (3.1)            |         |
| 4, dirty infected    | 35 (1.5)     | 1 (3.6)          | 34 (1.5)            |         |
| **ASA classification** |            |                  |                     | .75     |
| 1, no disturb        | 28 (1.2)     | 0 (0)            | 28 (1.2)            |         |
| 2, mild disturb      | 467 (19.8)   | 5 (17.9)         | 462 (19.6)          |         |
| 3, severe disturb    | 1690 (71.7)  | 20 (71.4)        | 1670 (71.7)         |         |
| 4, life threat       | 169 (7.2)    | 3 (10.7)         | 166 (7.1)           |         |
| **Flap types (CPT code)** |          |                  |                     | .02     |
| 1, muscle (15756)    | 731 (31.0)   | 8 (28.6)         | 723 (31.1)          |         |
| 2, skin (15757)      | 1131 (48.0)  | 11 (39.3)        | 1120 (48.1)         |         |
| 3, fascial (15758)   | 436 (18.5)   | 7 (25)           | 429 (18.4)          |         |
| 4, fibula (20955)    | 49 (2.1)     | 0 (0)            | 49 (2.1)            |         |
| 5, iliac crest (20956) | 1 (0.0)  | 0 (0)            | 1 (2.1)             |         |
| 6, bone flap other than iliac crest (20962) | 8 (0.3) | 2 (7.1) | 6 (0.3) |         |
| **Tracheostomy**     | 814 (34.6)   | 13 (46.4)        | 801 (34.4)          | .18     |
| **Lymph node dissection** | 1255 (53.3) | 18 (64.3) | 1237 (53.1) | .24 |
| **Intraoperative/72 h postoperative transfusion** | 580 (24.6) | 15 (53.6) | 565 (24.3) | <.01 |

(continued)
after head and neck reconstructive procedures for cancers can be challenging. This is in part because of significant variation in endpoint definition(s). In this study, a postoperative mortality rate of 1.5% was identified after microsurgical head and neck cancer reconstruction. This is consistent with other published rates. A single-institution study reported an overall mortality rate of 0.88% and in-hospital mortality rate of 1.84%. Another review of 804 patients undergoing head and neck free flaps over 19 years reported 1.0% 30-day postoperative mortality. However, the rate increased to 5.2% when they stratified patients who were never discharged out of the hospital. Our study is unique. The data were obtained from multiple anonymous institutions instead of data reported by a single or group of numerous operating surgeon(s) from single institutions.

Although we found several associations on univariate analysis, preoperative anemia was the only independent risk factor for 30-day postoperative mortality based on multivariable analysis. Other studies have described advanced age, prolonged operative time, frailty, and preoperative weight loss as predictors of postoperative mortality. Advanced age >80 years has been defined as an important determinant of postoperative morbidity and mortality. Although the patients who died were generally older in our study, we did not find age >80 years to be an independent risk predictor of death. Similarly, a systematic review of head and neck reconstruction under age 65 years did not find age a determinant of mortality. Increased operative time has been previously found to be associated with higher postoperative complications. However, we did not find a prolonged operative time of >9 hours to be associated with increased 30-day mortality. The frailty index using the NSQIP database has been validated to predict postoperative morbidity and mortality; we did not find 5-factor modified frailty index as a determinant of mortality, however. Crippen et al reported preoperative weight loss and underweight status as risk factors for postoperative mortality. Among their cohort, the proportion of patients in the underweight category with anemia was highly prevalent.

Preoperative anemia is a well-known, poor prognostic factor in cancer patients. Paumeister et al described anemia as a paraneoplastic syndrome in head and neck squamous cell carcinoma and an independent prognostic marker. In this study, the World Health Organization (WHO) definition of anemia was used (hemoglobin of <12 g/dL in females and <13 g/dL in males). Since the ACS NSQIP database does not report hemoglobin, we converted hemoglobin values to equivalents in hematocrit (%). Preoperative anemia is known to be associated with increased postoperative complications after head and neck oncologic surgery. This study, however, is the first to identify preoperative anemia as an independent risk factor for 30-day postoperative mortality in these patients and further characterized the degree of anemia (ie, hematocrit <30% regardless of gender) to be associated with 30-day mortality independent of malnutrition.

This finding of preoperative anemia as an independent risk factor for 30-day postoperative mortality has practical implications for a microsurgeon. When evaluating an anemic patient, surgeons typically use a hematocrit of <21% as a transfusion threshold. However, in our sample, there were no patients with such a low level of hematocrit. Hence, we could not evaluate the association of critically low preoperative hematocrit and mortality. The WHO cutoff for anemia of <36% is generally not low enough for microsurgeons to consider preoperative blood transfusion. Similarly, intraoperative transfusion is mainly determined by the length of the operation and amount of blood loss rather than a specific hematocrit level. This may need additional consideration. This study has identified convincing data showing that a hematocrit of <30% is the single independent preoperative risk factor from among the multitude of risk factors that affect 30-day postoperative mortality in patients undergoing microsurgical head and neck cancer reconstruction. Hence, preoperative anemia warrants a significant consideration before embarking on a microsurgical head and neck reconstruction.

A quarter (26%) of patients in this national cohort undergoing microsurgical head and neck reconstruction for cancer needed an intraoperative or 72-hour postoperative transfusion. This is consistent with the current literature. A single-institution study of 167 patients undergoing free flap reconstruction for head and neck cancer found a 53.9% transfusion rate. They reported an association between transfusions of greater than or equal to 3 units of blood and risk of postoperative death. The findings from that study discourage the liberal
Importantly, it is the reconstruction that has been reported to have as high as a 26% transfusion rate compared with a 0% rate in patients not undergoing reconstruction. Understanding that preoperative anemia is a risk factor for mortality after microsurgical reconstruction allows the reconstructive team to optimize such patients preoperatively to mitigate the risk of 30-day postoperative mortality. Microsurgeons should use their discretion or work together with the oncologist in determining the underlying etiology of anemia. Although blood transfusion has its risks, its benefits in optimizing patients preoperatively should not be undermined. If anemia is caused by iron deficiency, then preoperative iron supplementation has been shown to have favorable outcomes. Furthermore, anemia can be linked to

| Variable | Odds ratio [95% confidence interval] | P value |
|----------|-------------------------------------|---------|
| Advanced age\(^b\) | 2.88 [1.08-7.68] | .03 |
| Obesity vs normal BMI\(^c\) | 1.01 [0.37-2.80] | .99 |
| Male sex | 1.43 [0.61-3.38] | .42 |
| Minority race | 1.16 [0.34-3.93] | .81 |
| Plastic surgeon | 0.56 [0.19-1.64] | .30 |
| Diabetes | 1.69 [0.68-4.19] | .26 |
| Current smoking | 0.61 [0.25-1.51] | .28 |
| Dyspnea | 1.63 [0.49-5.48] | .42 |
| Poor functional status | 5.94 [1.73-20.37] | <.01 |
| Ventilator dependence | — | — |
| COPD | 0.49 [0.07-3.64] | .49 |
| Ascites | — | — |
| CHF | — | — |
| Hypertension | 2.32 [1.04-5.14] | .04 |
| Renal failure | — | — |
| Dialysis | — | — |
| Disseminated cancer | 1.65 [0.49-5.52] | .42 |
| Preoperative wound infection | 2.71 [1.02-7.21] | .046 |
| Chronic steroid use | 1.77 [0.41-7.56] | .44 |
| Preoperative weight loss | 1.29 [0.39-4.31] | .68 |
| Bleeding disorder | 1.88 [0.25-14.13] | .54 |
| Preoperative transfusion | — | — |
| Chemotherapy | — | — |
| Radiotherapy | — | — |
| High modified frailty index score (mFI >2)\(^d\) | 2.23 [0.30-16.81] | .44 |
| Renal insufficiency\(^e\) | 3.24 [1.39-7.58] | <.01 |
| Malnutrition\(^f\) | 4.54 [1.30-15.82] | .02 |
| Anemia\(^g\) | 4.81 [2.01-11.49] | <.01 |
| Thrombocytopenia\(^h\) | 2.07 [0.71-6.04] | .19 |
| Advanced wound class | 2.49 [0.74-8.38] | .14 |
| Advanced ASA class | 1.23 [0.46-3.25] | .68 |
| Prolonged operating time | 2.56 [1.15-5.68] | .02 |
| Tracheostomy | 1.65 [0.78-3.49] | .19 |
| Lymph node dissection | 1.59 [0.73-3.45] | .24 |
| Bone flap | 3.12 [0.72-13.47] | .13 |
| Emergency procedure | — | — |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

\(^a\)Bold indicates statistical significance P < .05.
\(^b\)Advanced age >80 years.
\(^c\)Normal BMI 18.5 kg/m\(^2\) to 24.9 kg/m\(^2\), obesity BMI >30.0 kg/m\(^2\).
\(^d\)High modified frailty index, mFI >2.
\(^e\)Renal insufficiency, creatinine <1.2 g/dL.
\(^f\)Malnutrition, albumin <3.5 g/dL.
\(^g\)Anemia, hematocrit <36% for female, hematocrit <39% for male.
\(^h\)Thrombocytopenia, platelets <150,000/mm\(^3\).
Table 3. Multivariable Logistic Regression.

| Risk factor                     | Model 1 (AUC = 0.89) | P value | Model 2 (AUC = 0.90) | P value | Model 3 (AUC = 0.90) | P value | Model 4 (AUC = 0.91) | P value |
|--------------------------------|----------------------|---------|----------------------|---------|----------------------|---------|----------------------|---------|
|                                | adjusted OR [95% CI] |         | adjusted OR [95% CI] |         | adjusted OR [95% CI] |         | adjusted OR [95% CI] |         |
| Age >80 y                       | 1.24 [0.14-11.14]    | .85     | 1.89 [0.20-17.64]    | .58     | 1.20 [0.14-10.41]    | .87     | 1.81 [0.19-16.87]    | .60     |
| Hypertension                    | 1.75 [0.43-7.17]     | .44     | 2.06 [0.50-8.47]     | .32     | 1.87 [0.44-7.87]     | .40     | 2.01 [0.48-8.41]     | .34     |
| Dependent functional status     | 0.78 [0.05-11.12]    | .83     | 1.55 [0.11-22.94]    | .99     | 0.47 [0.03-7.94]     | .97     | 0.70 [0.03-16.08]    | .98     |
| Preoperative wound infection    | 0.79 [0.09-6.80]     | .55     | 0.86 [0.10-7.60]     | .89     | 0.75 [0.09-6.61]     | .80     | 0.99 [0.12-8.49]     | .99     |
| Renal insufficiency             | 1.53 [0.37-6.32]     | .34     | 2.16 [0.51-9.12]     | .29     | 6.96 [0.70-69.17]    | .10     | 6.45 [0.60-69.25]    | .12     |
| Malnutrition                    | 1.87 [0.51-6.89]     | .93     | 9.59 [2.32-39.65]    | <.01    | 24.58 [1.79-337.33]  | .01     | 11.64 [3.06-44.25]   | <.01    |
| Anemia                          | 22.34 [1.62-308.10]  | .11     | 3.81 [0.77-18.85]    | .10     | 4.45 [0.89-22.38]    | .07     | 5.05 [0.94-27.07]    | .06     |

Abbreviations: AUC, area under the curve; CI, confidence interval; OR, odds ratio.

aAUC indicates discrimination of the model in patients who did and not experience 30-day mortality. The interaction term for anemia and malnutrition was not significant (P > .05). Bold indicates statistical significance P < .05.

bModel 1 = albumin < 3.5 g/dL and hematocrit < 36% for female, hematocrit < 39% for male.

cModel 2 = albumin < 3.5 g/dL and hematocrit < 30% for both female and male.

dModel 3 = albumin < 2.5 g/dL and hematocrit < 36% for female, hematocrit < 39% for male.

eModel 4 = albumin < 2.5 g/dL and hematocrit < 30% for both female and male.

fFirth penalized likelihood estimates reported due to the small number of event.
the manuscript; Venus Barlas, study design, manuscript writing, reviewed manuscript, agreed with contents, finally approved the manuscript; Timothy R. Petersen, analysis, data presentation, reviewed manuscript, agreed with contents, finally approved the manuscript; Nathan G. Menon, study design, manuscript writing, and editing, reviewed manuscript, agreed with contents, finally approved the manuscript; Nathan T. Morrell, study design, manuscript writing and editing, reviewed manuscript, agreed with contents, finally approved the manuscript.

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