AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

OTO Open
2021, Vol. 5(3) 1–8

DOI: 10.1177/2473974X211037257
http://oto-open.org
SAGE

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

Barkat Ali, MD, DABS[1], EunHo Eunice Choi, MS[2], Venus Barlas[3], Timothy R. Petersen, PhD[4], Nathan G. Menon, MD[5], and Nathan T. Morrell, MD[5]

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

Received July 15, 2021; accepted July 15, 2021.

Postoperative mortality after microsurgical head and neck cancer reconstruction is a devastating complication with varying incidences.[1-4] 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

[1]Department of Surgery, Division of Plastic and Reconstructive Surgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[2]Biostatistics, Epidemiology, and Research Designs, Clinical and Translational Science Center, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[3]University of New Mexico, School of Medicine, Albuquerque, New Mexico, USA
[4]Department of Anesthesia and Critical Care, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[5]Department of Orthopedics, Hand, and Microsurgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

Corresponding Author:
Barkat Ali, MD, DABS, Division of Plastic and Reconstructive Surgery, University of New Mexico, MSC 10 5610, 1 University of New Mexico, Albuquerque, New Mexico 87131, USA.
Email: bali@salud.unm.edu

been made that have improved the safety and efficacy of these procedures.[5,6] Historically, microsurgical flap survival has been considered the hallmark of success in head and neck reconstruction.[7] Although technical and procedural factors hold primacy to the success of microsurgical reconstruction, patient-related risk factors mainly determine postoperative mortality.[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.[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.[a]

	Total, n (%), 2356	Mortality, n (%), 28 (1.2)	No mortality, n (%), 2328 (98.81)	*P* value
Age, y, median (IQR)	**63, 55-72**	**71, 60-76**	**63, 55-71**	**<.01**
BMI, kg/m^2, 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
Presepsis	21 (0.9)	0 (0)	21 (0.9)	>.99
Renal insufficiency	**276 (12.9)**	**8 (32)**	**268 (12.7)**	**<.01**
Malnutrition	206 (18.3)	5 (50)	201 (18.1)	.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**
Cancer site				.24
1, oral cavity	1121 (47.6)	10 (35.7)	1211 (52.0)	
2, pharynx	183 (7.8)	4 (14.3)	179 (7.7)	
3, larynx	164 (7)	1 (3.6)	163 (7)	

(continued)

Table 1. (continued)

	Total, n (%), 2356	Mortality, n (%), 28 (1.2)	No mortality, n (%), 2328 (98.81)	*P* value
4, nasal cavity and paranasal sinuses	94 (4)	2 (7.1)	92 (4)	
5, salivary glands	78 (3.3)	1 (3.6)	77 (3.3)	
6, skin, soft tissue, bones of face	616 (26.1)	10 (35.7)	606 (26.0)	
Mean operating time, min, mean ± SD	**538.66 ± 195.10**	**657.6 ± 219.9**	**537.2 ± 194.4**	**<.01**

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPT code, Current Procedural Terminology code; IQR, interquartile range.
[a]High modified frailty index, mFI >2; renal insufficiency, creatinine <1.2 g/dL; malnutrition, albumin <3.5 g/dL; anemia, hematocrit <36% for female, hematocrit <39% for male; thrombocytopenia, platelets <150,000/mm^3. Bold indicates statistical significance $P < .05$.

after head and neck reconstructive procedures for cancers can be challenging. This is in part because of significant variation in endpoint definition(s).[4,5,10,11] 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%.[2] 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.[3] 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.[3,10,12-16] Advanced age >80 years has been defined as an important determinant of postoperative morbidity and mortality.[10,12] 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.[17] Increased operative time has been previously found to be associated with higher postoperative complications.[3,13,14] 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.[15] Crippen et al[16] 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.[18,19] Baumeister et al[20] 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).[8,9] 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.[21-24] 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.[25] 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.[26] 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

Table 2. Univariate Logistic Regression.[a]

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.

use of transfusion.[27] 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.[28] 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.[29] If anemia is caused by iron deficiency, then preoperative iron supplementation has been shown to have favorable outcomes.[30] Furthermore, anemia can be linked to

Table 3. Multivariable Logistic Regression.[a]

Risk factor	Model 1 (AUC = 0.89)[b] adjusted OR [95% CI]	*P* value	Model 2 (AUC = 0.90)[c] adjusted OR [95% CI]	*P* value	Model 3 (AUC = 0.90)[d] adjusted OR [95% CI]	*P* value	Model 4 (AUC = 0.91)[e] adjusted OR [95% CI]	*P* value
Age >80 y	1.24 [0.14-11.14]	.85	1.89 [0.20-17.64]	.58	1.20 [0.14-10.41]	0.87	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]	0.40	2.01 [0.48-8.41]	.34
Dependent functional status	0.78 [0.05-11.12][f]	.98	1.55 [0.11-22.94][f]	.99	0.47 [0.03-7.94][f]	0.97	0.70 [0.03-16.08][f]	.98
Preoperative wound infection	0.79 [0.09-6.80]	.83	0.86 [0.10-7.60]	.89	0.75 [0.09-6.61]	0.80	0.99 [0.12-8.49]	.99
Renal insufficiency	1.53 [0.37-6.32]	.55	1.57 [0.36-6.84]	.55	1.59 [0.38-6.61]	0.53	1.57 [0.35-7.01]	.56
Malnutrition	1.87 [0.51-6.89]	.34	2.16 [0.51-9.12]	.29	6.96 [0.70-69.17]	0.10	6.45 [0.60-69.25]	.12
Anemia	22.34 [1.62-308.10][f]	.93	**9.59 [2.32-39.65]**	**<.01**	24.58 [1.79-337.33][f]	0.93	**11.64 [3.06-44.25]**	**<.01**
Prolonged operating time	3.59 [0.74-17.51]	.11	3.81 [0.77-18.85]	.10	4.45 [0 .89-22.38]	0.07	5.05 [0.94-27.07]	.06

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

[a]AUC 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 $P < .05$.

[b]Model 1 = albumin <3.5 g/dL and hematocrit <36% for female, hematocrit <39% for male.

[c]Model 2 = albumin <3.5 g/dL and hematocrit <30% for both female and male.

[d]Model 3 = albumin <2.5 g/dL and hematocrit <36% for female, hematocrit <39% for male.

[e]Model 4 = albumin <2.5 g/dL and hematocrit <30% for both female and male.

[f]Firth penalized likelihood estimates reported due to the small number of events.

preoperative malnutrition, in which case improving nutritional status will synergistically reduce complications of malnutrition and 30-day postoperative mortality. Indeed, mortality was worse in our study when anemia was coupled with lower albumin levels.[31] In this study, there were no patients with hematocrit less than 21. Therefore we are not able to analyze the severely anemia patients.

Given the database's multi-institutional nature and large sample size, the mortality rate reported is the best representation of 30-day postoperative mortality. However, this database is not without limitation. Although the findings help us generate a hypothesis, the retrospective nature of the study does not allow us to test it because of the lack of granularity in the database. The relative paucity of bone flap in our study introduces bias. The reason for this is in part because of our strict selection criterion of including patients with primary head and neck cancers only. White race constituted the majority of sample, which further limits the generalizability of the our results. Being a retrospective study, a cause-and-effect relationship cannot be ascertained. Because the cause of death is not reported in the data set, we did not include other complications in our study other than death. Intraoperative and 72-hour postoperative transfusion may have significant overlap with mortality, rendering it not mutually exclusive and hence statistically inappropriate to draw an association. This is why we did not adjust for this in our multivariable logistic regression.

However, given the extensive preoperative variables and the robust statistical analysis performed, powered associations between preoperative anemia and 30-day postoperative mortality have been established. Furthermore, the variables not reported in the database were not included in the analysis and hence remained unknown confounders. We included an extensive set of variables and developed logistic regression models of risk stratifying to quantify the magnitude of this problem.

Conclusions

Recognizing that preoperative anemia is an independent risk factor for 30-day postoperative mortality in microsurgical head and neck cancer reconstruction is important for both patients and surgeons before undertaking such a reconstructive path. Using this information during informed consent, preoperative optimization, and resource allocation can help mitigate the risk of mortality. Further investigations are needed to define precise levels of anemia and rehabilitation protocols to correct to minimize the risk of 30-day postoperative mortality.

Authors' Note

The findings and conclusions are drawn as a result of the statistical analysis by the authors and were not verified by the ACS NSQIP.

Author Contributions

Barkat Ali, data acquisition, study design, manuscript writing, reviewed manuscript, agreed with contents, finally approved the manuscript; **EunHo Eunice Choi**, data analysis, manuscript writing, reviewed manuscript, agreed with contents, finally approved

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.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

Supplemental Material

Additional supporting information is available at https://journals.sagepub.com/doi/suppl/10.1177/2473974X211037257.

References

1. Lahtinen S, Koivunen P, Ala-Kokko T, et al. Short- and long-term mortality and causes of death after reconstruction of cancers of the head and neck with free flaps. *Br J Oral Maxillofac Surg*. 2019;57:21-28.
2. Tanaka K, Sakuraba M, Miyamoto S, et al. Analysis of operative mortality and postoperative lethal complications after head and neck reconstruction with free tissue transfer. *Jpn J Clin Oncol*. 2011;41:758-763.
3. Pohlenz P, Klatt J, Schmelzle R, Li L. The importance of in-hospital mortality for patients requiring free tissue transfer for head and neck oncology. *Br J Oral Maxillofac Surg*. 2013;51:508-513.
4. Brady JS, Desai SV, Crippen MM, et al. Association of anesthesia duration with complications after microvascular reconstruction of the head and neck. *JAMA Facial Plast Surg*. 2018;20:188-195.
5. Seidenberg B, Rosznak SS, Hurwitt ES, et al. Immediate reconstruction of the cervical esophagus by a revascularized isolated jejunal segment. *Ann Surg*. 1959;149:162-171.
6. McLean D, Buncke H. Autotransplant of omentum to a large scalp defect, with microsurgical revascularization. *Plast Reconstr Surg*. 1972;49:268-274.
7. Lueg EA. Comparing microvascular outcomes at a large integrated health maintenance organization with flagship centers in the United States. *Arch Otolaryngol Head Neck Surg*. 2004;130:779-785.
8. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5-37.
9. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107:1747-150. doi:10.1182/blood-2005-07-3046
10. Vaz JA, Côté DW, Harris JR, Seikaly H. Outcomes of free flap reconstruction in the elderly. *Head Neck*. 2013;35:884-888.
11. Joo YH, Cho KJ, Park JO, Kim SY, Kim MS. Surgical morbidity and mortality in patients after microvascular reconstruction for head and neck cancer. *Clin Otolaryngol*. 2018;43:502-508.
12. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. *J Am Coll Surg*. 2006;203:865-877.
13. Wong AK, Joanna Nguyen T, Peric M, et al. analysis of risk factors associated with microvascular free flap failure using a multi-institutional database. *Microsurgery*. 2015;35:6-12.
14. Offodile AC II, Aherrera A, Wenger J, Rajab TK, Guo L. Impact of increasing operative time on the incidence of early failure and complications following free tissue transfer? A risk factor analysis of 2,008 patients from the ACS-NSQIP database. *Microsurgery*. 2017;37:12-20.
15. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-factor modified frailty index using American College of Surgeons NSQIP data. *J Am Coll Surg*. 2018;226:173-181.e8.
16. Crippen MM, Brady JS, Mozeika AM, Eloy JA, Baredes S, Park RCW. Impact of body mass index on operative outcomes in head and neck free flap surgery. *Otolaryngol Head Neck Surg*. 2018;159:817-823.
17. Goh CS, Kok YO, Yong CP, et al. Outcome predictors in elderly head and neck free flap reconstruction: a retrospective study and systematic review of the current evidence. *J Plast Reconstr Aesthet Surg*. 2018;71:719-728.
18. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*. 2001;91:2214-2221.
19. Kumar P. Impact of anemia in patients with head and neck cancer. *Oncologist*. 2000;5(suppl 2):13-18.
20. Baumeister P, Canis M, Reiter M. Preoperative anemia and perioperative blood transfusion in head and neck squamous cell carcinoma. *PLoS One*. 2018;13:e0205712.
21. Abt NB, Tarabanis C, Miller AL, Puram SV, Varvares MA. Preoperative anemia displays a dose-dependent effect on complications in head and neck oncologic surgery. *Head Neck*. 2019;41:3033-3040.
22. Haidar YM, Kuan EC, Verma SP, Goddard JA, Armstrong WB, Tjoa T. Free flap versus pedicled flap reconstruction of laryngopharyngeal defects: a 10-year national surgical quality improvement program analysis. *Laryngoscope*. 2019;129:105-112.
23. Chen MH, Chang PM, Chen PM, et al. Prognostic significance of a pretreatment hematologic profile in patients with head and neck cancer. *J Cancer Res Clin Oncol*. 2009;135:1783-1790.
24. Mulvey CL, Brant JA, Bur AM, et al. Complications associated with mortality after head and neck surgery. *Otolaryngol Head Neck Surg*. 2017;156:504-510.
25. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340:409-417.
26. Krupp NL, Weinstein G, Chalian A, Berlin JA, Wolf P, Weber RS. Validation of a transfusion prediction model in head and neck cancer surgery. *Arch Otolaryngol Head Neck Surg*. 2003;129(12):1297-1302.
27. Danan D, Smolkin ME, Varhegyi NE, Bakos SR, Jameson MJ, Shonka DC Jr. Impact of blood transfusions on patients with head

and neck cancer undergoing free tissue transfer. *Laryngoscope*. 2015;125(1):86-91.

28. Rogers SN, Horisk K, Groom P, Lowe D. Management of anaemia and blood in patients having neck dissections or free flaps for head and neck cancer. *Br J Oral Maxillofac Surg*. 2019; 57(6):543-549.
29. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine: first of two parts—blood transfusion. *N Engl J Med*. 1999;340(6):438-447.
30. Janssen TL, Steyerberg EW, van Gammeren AJ, Ho GH, Gobardhan PD, van der Laan L. Intravenous iron in a prehabilitation program for older surgical patients: prospective cohort study. *J Surg Res*. 2021;257:32-41.
31. Durrand J, Singh SJ, Danjoux G. Prehabilitation. *Clin Med (Lond)*. 2019;19(6):458-464. doi:10.7861/clinmed.2019-0257