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ORIGINAL RESEARCH

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Sarcopenia is associated with blood transfusions in head and neck cancer free flap surgery

Alexander Joseph Jones MD[1] | Vincent J. Campiti BS[1] | Mohamedkazim Alwani MD[1] | Leah J. Novinger MD, PhD[1] | Brady Jay Tucker BS[1] | Andrea Bonetto PhD[2] | Jessica A. Yesensky MD[1] | Michael W. Sim MD[1] | Michael G. Moore MD[1] | Avinash V. Mantravadi MD[1]

[1]Department of Otolaryngology–Head and Neck Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence
Alexander Joseph Jones, 1130 West Michigan Street, Fesler Hall 400, Indianapolis, IN 46202.
Email: jonesalj@indiana.edu

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Abstract

Objective: To determine if sarcopenia is a predictor of blood transfusion requirements in head and neck cancer free flap reconstruction (HNCFFR).

Methods: A single-institution, retrospective review was performed of HNCFFR patients with preoperative abdominal imaging from 2014 to 2019. Demographics, comorbidities (modified Charlson Comorbidity Index [mCCI]), skeletal muscle index (cm^2/m^2), oncologic history, intraoperative data, and 30-day postoperative complications (Clavien-Dindo score [CD]) were collected. Binary logistic regression was performed to determine predictors of transfusion.

Results: Eighty (33.5%), 66 (27.6%), and 110 (46.0%) of n = 239 total patients received an intraoperative, postoperative, or any perioperative blood transfusion, respectively. Sixty-two (25.9%) patients had sarcopenia. Patients receiving intraoperative transfusions had older age (P = .035), more frequent alcoholism (P = .028) and sarcopenia (P < .001), greater mCCI (P < .001), lower preoperative hemoglobin (P < .001), reconstruction with flaps other than forearm (P = .003), and greater operative times (P = .001), intravenous fluids (P < .001), and estimated blood loss (EBL, P < .001). Postoperative transfusions were associated with major complications (CD ≥ 3; P < .001). Multivariate regression determined sarcopenia (P = .023), mCCI (P = .013), preoperative hemoglobin (P = .002), operative time (P = .036), and EBL (P < .001) as independent predictors of intraoperative transfusion requirements. Postoperative transfusions were predicted by preoperative hemoglobin (P = .007), osseous flap (P = .036), and CD ≥ 3 (P < .001). A perioperative transfusion was predicted by sarcopenia (P = .021), preoperative hemoglobin (P < .001), operative time (P = .008), and CD ≥ 3 (P = .018).

Conclusion: Sarcopenia is associated with increased blood transfusions in HNCFFR. Patients should be counseled preoperatively on the associated risks, and the

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increased blood product requirement should be accounted in resource-limited scenarios.

Level of Evidence: 4.

KEYWORDS
blood transfusion, free flap reconstruction, head and neck cancer, sarcopenia, skeletal muscle index

1 | INTRODUCTION

Microvascular free flap reconstruction (FFR) is often the standard repair method after resection of advanced head and neck cancer (HNC). Free flaps are versatile and provide adequate tissue volume for restoration of both form and function after oncologic ablation. However, these procedures are often extensive in tissue removal, operative time, and utilization of medical resources including blood products.

The indications for blood product transfusion remain controversial, particularly in head and neck reconstruction where there is a paucity of quality studies. For patients without significant coronary disease, the current precept of transfusing is indicated with significant active bleeding and/or hemoglobin (Hgb) < 7 g/dL (hematocrit <21%),[1] the standard to which our institution also adheres.

Both administering and withholding transfusions have unique risks. In the acute setting, significant anemia carries the hazard of ischemia and tissue injury from inadequate oxygen delivery, potentially resulting in myocardial infarctions, cerebrovascular accidents, acute kidney injury, and ischemic hepatitis.[2] Significant anemia could also lead to flap failure, although this association has not been identified.[1,3,4] Conversely, transfusing carries risk of adverse consequences including allergic reactions, acute- and delayed-hemolysis, transfusion-associated cardiac overload, transfusion-related lung injury, and transmission of viral pathogens.[2] Within both head and neck and plastic surgery FFR disciplines, transfusions have been associated with greater postoperative complications,[5,6] wound complications,[6] and unplanned readmission.[7] Also, transfusions in oncologic resection have been associated with earlier cancer recurrence and worse overall survival.[8,9] These in conjunction with the significant financial cost and limited availability of blood products necessitate careful consideration for those patients to whom transfusions are provided.

Preoperative identification of patients at risk for transfusion in FFR would enable surgeons to provide better preoperative counseling and address blood product availability. An emerging preoperative risk factor being analyzed is sarcopenia, which is the combination of low muscle strength, low muscle quantity or quality, and low physical performance.[10] Its etiology includes aging, inactivity, malnutrition, inflammation, and cancer cachexia.[10] Sarcopenia can be assessed objectively on radiologic measurements of skeletal muscle mass (SMM) and/or physical assessments of mobility and strength.[10] However, radiologically determined sarcopenia alone has substantial medical implications, especially in the surgical and oncologic specialties where computed tomography (CT) imaging is frequently obtained.[11-19] Within HNC resection and FFR, preoperative CT-determined sarcopenia has demonstrated prognostic for complications and overall survival.[20-27]

In addition to the overall reduced SMM, sarcopenic patients have reduced skeletal muscle capillary density and exercise capacity.[28] Furthermore, skeletal muscle requires substantial vascular supply and blood-holding capacity for exercise demands.[29] Because of these, we hypothesize that sarcopenic patients have reduced total blood volume compared to nonsarcopenic patients. As a result, they may experience greater proportional blood loss and increased transfusion requirements from surgery.[30-33] To delineate this relationship and identify those patients at risk for transfusion, we sought to investigate sarcopenia and its effect on transfusion requirements with head and neck cancer free flap reconstruction (HNCFFR) where transfusions are highly prevalent.

2 | METHODS

After obtaining Institutional Review Board approval, a retrospective, single-center study was conducted at our tertiary referral center. Adult patients undergoing HNCFFR from January 1, 2014 through December 31, 2019 were collected. Subjects with pathologically confirmed head and neck malignancy and adequate 90-day preoperative CT imaging of the abdomen were included for review. Patients with synchronous cancers, distant metastatic disease, immunodeficiency (ie, HIV), or bleeding disorders were excluded.

Patient demographics, modified Charlson Comorbidity Index (mCCI),[34,35] cancer data and staging according to the eighth edition American Joint Committee on Cancer (AJCC) Cancer Staging Manual,[36] prior chemotherapy or radiation therapy, preoperative Hgb, intraoperative details, and 30-day postoperative courses were collected. Red blood cell transfusions were classified as intraoperative, 30-day postoperative, or perioperative after combining both intra- and postoperative timelines. Malignancy occupying the oral cavity, oropharynx, hypopharynx, and/or larynx were collectively grouped as aerodigestive. Tumors located within the nasal cavity, paranasal sinuses, nasopharynx, major salivary glands, thyroid, parathyroid, or cutaneous areas were categorized as non-aerodigestive. The mCCI was calculated by the summation of the patient comorbidities. The calculation provided a weight of: 1.0 for hypertension, diabetes mellitus, coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular accident (CVA), chronic obstructive pulmonary

disease (COPD), peripheral vascular disease (PVD), and connective tissue disorder; 2.0 for chronic kidney disease; and 3.0 for liver failure or cirrhosis.[34,35] Postoperative complications were categorized according to the Clavien-Dindo (CD) classification. Those involving surgical or radiologic intervention, single- or multiorgan dysfunction, intensive care unit (ICU) management, or death were grouped as major complications (CD ≥ 3).[37]

Skeletal muscle index (SMI, cm^2/m^2) was calculated as previously described using SliceOmatic v5.0 software (TomoVision, Magog, Canada).[20] Sarcopenia was determined as <41.6 cm^2/m^2 for males and <32.0 cm^2/m^2 for females.[38] Figure 1 provides a comparative example of these measurements in a sarcopenic (A) and a non-sarcopenic (B) patient.

Statistical analyses were performed using SPSS v26.0 (IBM Inc., Armonk, New York). Nominal data were displayed as percentages and analyzed with two-sided Pearson's χ^2 or Fisher's exact tests. Ordinal data were written as mean ± SD and analyzed using two-sided Welch's *t* test or Mann-Whitney *U* test. Statistical significance was determined at $P < .05$. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for nominal variables.

Simple binary logistic regression analyses were performed for each independent variable on intraoperative, postoperative, and perioperative transfusion requirements. Significant variables on univariate regression were then included in the multivariate regression using the backward Wald method to identify independent predictors of transfusion requirements. Adjusted *P* values and ORs were calculated for those factors that remained significant in the final multivariate binary logistic regression model.

3 | RESULTS

3.1 | Cohort summary

A summary of the patient demographics, comorbidities, and intraoperative data can be found in Table 1. A total of 239 patients were included, which consisted predominantly of white (94.6%) males (68.21%) with average age of 60.4 ± 13.7 years and body mass index (BMI) of 25.7 ± 7.6 kg/m^2. Significant smoking and alcohol abuse were present in 71.5% and 31.8% of patients, respectively. At least one major comorbidity (mCCI ≥ 1) was present in 62.8% of the cohort. Sarcopenia afflicted 25.9% of the study group. Most patients presented with advanced-stage (stage III-IV, 85.7%) squamous cell carcinoma (81.2%) of the aerodigestive tract (72.0%), 31.0% of whom had undergone prior chemotherapy and/or radiation therapy. Reconstruction utilized anterolateral thigh (36.8%), forearm (26.8%), fibula (19.7%), or other (16.7%) free flaps. Of these, 33.5% included an osseous component. The mean preoperative Hgb was 12.9 ± 1.9 mg/dL. Patients had an average operative time of 637 ± 169 minutes, were administered 5213 ± 2216 mL of intravenous fluids (IVF), and had EBL of 386 ± 335 mL. An intraoperative red blood cell transfusion was provided in 33.5% of patients.

The 30-day postoperative course is summarized in Table 2. A postoperative transfusion was provided to 66 patients (27.6%). The most frequent major complications after HNCFFR included returning to the operating room (17.2%), fistula (15.5%), and major pulmonary events (pneumonia, reintubation, or mechanical ventilation >48 hours; 12.6%). These often resulted in a prolonged stay (>48 hours) within the ICU (21.8%). Overall, 23.0% patients experienced a major complication (CD ≥ 3). Combining both intraoperative and 30-day postoperative courses, 110 (46.0%) individuals received a perioperative transfusion.

3.2 | Factors associated with transfusions

A comparison of intra- and postoperatively transfused and nontransfused patients are displayed in Tables 1 and 2, respectively. Those receiving a transfusion during surgery were older (62.9 ± 12.2 vs 59.2 ± 14.2, $P = .035$), sarcopenic (46.3% vs 15.7%, $P < .001$), with lower preoperative Hgb (12.0 ± 1.0 vs 13.5 ± 1.7 g/dL, $P < .001$), higher mCCI ($P < .001$), and more alcohol abuse (41.3% vs 27.0%, $P = .028$). No difference was noted between sex, race, BMI, smoking, cancer stage, histology, or chemoradiation histories. Intraoperative transfusions were associated with non-forearm flaps (85.0% vs 67.2%, $P = .003$), longer operative (691 ± 190 vs 610 ± 152 min, $P = .001$) and ischemia times (119 ± 55 vs 100 ± 45 min, $P = .022$), and greater IVF (5970 ± 2394 vs 4832 ± 2023 mL, $P < .001$) and EBL (614 ± 461 vs 273 ± 155 mL, $P < .001$).

Thirty-day postoperative transfusions were associated with postoperative complications. Specifically, a transfusion was more likely in those incurring a major pulmonary complication, (30.3% vs 5.8%, $P < .001$), major bleeding event (hemorrhage or hematoma; 13.6% vs

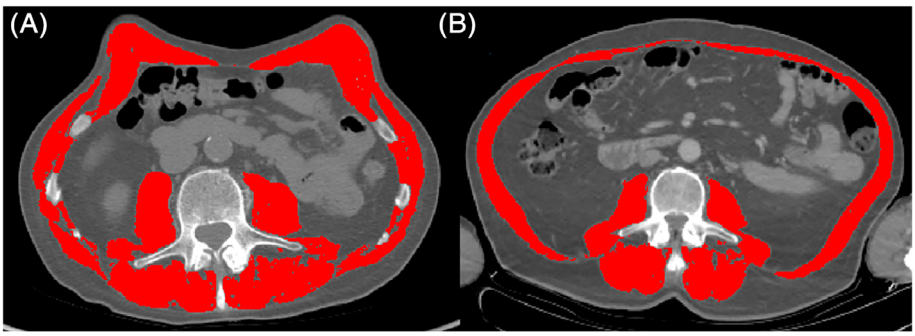

FIGURE 1 Axial CT comparison of a nonsarcopenic 47-year-old male with BMI of 21.0 kg/m^2 and SMI of 60.1 cm^2/m^2 (A) and a sarcopenic 54-year-old male with BMI of 20.2 kg/m^2 and SMI of 38.2 cm^2/m^2 (B). The highlighted areas indicate the isolated abdominal skeletal muscles at the third lumbar vertebra. BMI, body mass index; CT, computed tomography; SMI, skeletal muscle index

2.9%, $P = .003$), postoperative fistula (25.8% vs 11.6%, $P = .009$), flap failure (15.2% vs 0.6%, $P < .001$), return to operating room (42.4% vs 7.5%, $P < .001$), and prolonged ICU stay (48.5% vs 11.6%, $P < .001$). When accounting for all complications, those classified as major (CD ≥ 3) were more common in the postoperatively transfused group (50.0% vs 12.7%, $P < .001$).

TABLE 1 Cohort preoperative and intraoperative summary

Variable	All patients (n = 239)	Intraoperative transfusion		*P* value	OR (95% CI)
		No (n = 159)	Yes (n = 80)		
Age (y)	60.4 ± 13.7	59.2 ± 14.2	62.9 ± 12.2	**.035**[a]	
Sex (M)	68.2	69.2	66.3	.661[b]	0.90 (0.49-1.55)
Race (white)	94.6	95.6	92.5	.369[b]	0.57 (0.18-1.75)
BMI (kg/m^2)	25.7 ± 7.6	26.3 ± 7.7	24.6 ± 7.3	.088[a]	
Underweight	11.7	10.1	15.0	.290[b]	1.58 (0.71-3.52)
Normal	45.6	45.9	45.0	>.99[b]	0.96 (0.56-1.65)
Overweight	20.1	19.5	21.3	.736[b]	1.11 (0.57-2.16)
Obese	22.6	24.5	18.8	.331[b]	0.71 (0.36-1.38)
Sarcopenia	25.9	15.7	46.3	**<.001**[b]	**4.61 (2.50-8.51)**
Smoking	71.5	69.2	76.3	.289[b]	1.43 (0.77-2.65)
Alcohol	31.8	27.0	41.3	**.028**[b]	**1.89 (1.08-3.34)**
Diabetes	15.5	14.5	17.5	.572[b]	1.25 (0.61-2.59)
HTN	48.5	41.5	62.5	**.003**[b]	**2.35 (1.35-4.08)**
CVA	4.6	3.8	6.3	.514[b]	1.70 (0.50-5.75)
CAD	14.6	11.9	20.0	.121[b]	1.84 (0.89-3.81)
CHF	10.5	6.3	18.8	**.006**[b]	**3.44 (1.47-8.06)**
PVD	7.5	6.9	8.8	.611[b]	1.29 (0.48-3.47)
CKD	5.9	3.8	10.0	.077[b]	2.83 (0.95-8.47)
COPD	23.8	18.9	33.8	**.015**[b]	**2.19 (1.19-4.03)**
CT disorder	2.9	2.5	3.8	.689[b]	1.51 (0.33-6.92)
Liver failure	2.1	0.6	5.0	**.044**[b]	8.32 (0.91-75.68)
mCCI[e]				**<.001**[d]	
0	37.2	46.5	18.8	**<.001**[b]	**0.27 (0.14-0.50)**
1	23.4	23.3	23.8	>.99[b]	1.03 (0.55-1.93)
2	18.8	13.8	28.7	**.008**[b]	**2.51 (1.30-4.87)**
≥3	20.5	16.4	28.7	**.028**[b]	**2.06 (1.09-3.92)**
AJCC stage				.223[c]	
I-II	14.3	16.6	10.0	.239[b]	0.56 (0.24-1.30)
III	18.6	20.4	15.0	.379[b]	0.59 (0.33-1.43)
IV	67.1	63.1	75.0	.079[b]	1.76 (0.96-3.21)
Tumor histology (SCC)	81.2	79.9	83.8	.599[b]	1.30 (0.64-2.64)
Aerodigestive tumor	72.0	71.1	73.8	.761[b]	1.14 (0.62-2.09)
Prior Chemo/XRT	31.0	29.6	33.8	.554[b]	1.21 (0.68-2.16)
Free flap type				**.004**[c]	
ALT	36.8	35.2	40.0	.481[b]	1.23 (0.71-2.13)
Forearm	26.8	32.7	15.0	**.003**[b]	**0.36 (0.18-0.73)**
Fibula	19.7	20.1	18.8	.864[b]	0.92 (0.46-1.81)
Other	16.7	11.9	26.3	**.009**[b]	**2.62 (1.31-5.24)**
Flap tissue (osseous)	33.5	32.1	38.8	.316[b]	1.34 (0.77-2.35)
Operative time (min)	637 ± 169	610 ± 152	691 ± 190	**.001**[a]	
Ischemia time (min)[f]	106 ± 49	100 ± 45	119 ± 55	**.022**[a]	

(Continues)

TABLE 1 (Continued)

Variable	All patients (n = 239)	Intraoperative transfusion		*P* value	OR (95% CI)
		No (n = 159)	Yes (n = 80)		
IVF administered (mL)	5213 ± 2216	4832 ± 2023	5970 ± 2394	**<.001**[a]	
Preoperative Hgb (g/dL)	12.9 ± 1.9	13.5 ± 1.7	12.0 ± 1.9	**<.001**[a]	
EBL (mL)	386 ± 335	273 ± 155	614 ± 461	**<.001**[a]	

Note: Data presented as mean ± SD or percentage.
Significant analyses ($P < 0.05$) are listed in bold.
Abbreviations: AJCC, American Joint Committee on Cancer; ALT, anterolateral thigh; BMI, body mass index; CAD, coronary artery disease; Chemo/XRT, prior chemotherapy and/or radiation therapy; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; CT, connective tissue; CVA, cerebrovascular accident; EBL, estimated blood loss; Hgb, hemoglobin; HTN, hypertension; IVF, intravenous fluids; mCCI, modified Charlson Comorbidity Index; OR, odds ratio; PVD, peripheral vascular disease; RBC, red blood cells; SCC, squamous cell carcinoma.
[a]Welch's *t* test, two-sided.
[b]Fisher's exact test, two-sided.
[c]Pearson's χ^2 test, two-sided.
[d]Mann-Whitney *U* test, two-sided.
[e]Modified Charlson comorbidity index provided a weight of 1.0 for HTN, DM, CAD, CHF, CVA, COPD, PVD, and CT Disorder; 2.0 for CKD; and 3.0 for liver failure.
[f]Ischemia time was recorded for n = 183 patients: n = 122 without transfusion, n = 61 with transfusion.

TABLE 2 Postoperative complications and transfusions

Variable	All patients (n = 239)	Postoperative transfusion		*P* value	OR (95% CI)
		No (n = 173)	Yes (n = 66)		
Major cardiac event[c]	1.7	0.6	4.5	.065[a]	8.19 (0.84-80.20)
Major pulmonary event[d]	12.6	5.8	30.3	**<.001**[a]	**7.09 (3.10-16.20)**
Infectious complications					
SSI	17.6	15.6	22.7	.253[a]	1.59 (0.78-3.23)
Sepsis	2.5	1.2	6.1	.051[a]	5.52 (0.99-30.87)
CVA	1.3	0.6	3.0	.186[a]	5.38 (0.48-60.30)
ARI/ARF	0.4	0.0	1.5	.276[a]	N/A
Surgical complications					
Fistula	15.5	11.6	25.8	**.009**[a]	**2.65 (1.29-5.47)**
Flap failure	4.6	0.6	15.2	**<.001**[a]	**30.71 (3.85-245.3)**
Bleeding event[e]	5.9	2.9	13.6	**.003**[a]	**5.31 (1.71-16.49)**
Seroma	4.6	3.5	7.6	.182[a]	2.28 (0.67-7.75)
Chyle leak	2.5	1.7	4.5	.351[a]	2.70 (0.53-13.72)
Return to operating room	17.2	7.5	42.4	**<.001**[a]	**9.07 (4.30-19.14)**
Inpatient readmission	12.1	10.4	16.7	.190[a]	1.72 (0.77-3.87)
ICU stay					
Total (d)	3.0 ± 3.2	2.3 ± 1.2	5.0 ± 5.4	**<.001**[b]	
Prolonged (≥48 h)	21.8	11.6	48.5	**<.001**[a]	**7.20 (3.68-14.08)**
CD ≥ 3	23.0	12.7	50.0	**<.001**[a]	**6.86 (3.56-13.25)**

Note: Data presented as mean ± SD or percentage.
Significant analyses ($P < 0.05$) are listed in bold.
Abbreviations: ARI/ARF, acute renal insufficiency or acute renal failure; CD, Clavien-Dindo score; CI, confidence interval; CVA, cerebrovascular accident; ICU, intensive care unit; OR, odds ratio; SSI, surgical site infection.
[a]Fisher's exact test, two-sided.
[b]Mann-Whitney *U* test, two-sided.
[c]Major cardiac events include myocardial infarction and cardiac arrest.
[d]Major pulmonary events included pneumonia, reintubation, and prolonged (>48 hours) ventilator use.
[e]Bleeding event includes hematomas and hemorrhages (ie, carotid blowout).

TABLE 3 Binary logistic regression of intraoperative transfusion requirements

	Univariate		Multivariate	
Variable	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**
Sex (male)	.646	0.87 (0.49-1.55)		
Race (white)	.324	0.57 (0.18-1.75)		
Age (y)	**.046**	**1.02 (1.00-1.04)**		
BMI (kg/m^2)	**.097**	**0.97 (0.93-1.01)**		
Smoking	.254	1.43 (0.77-2.65)		
Alcohol	**.027**	**1.89 (1.08-3.34)**		
Sarcopenia	**<.001**	**4.61 (2.50-8.51)**	.023	3.34 (1.18-9.46)
mCCI (continuous)	**<.001**	**1.37 (1.16-1.62)**	.013	1.49 (1.09-2.05)
AJCC stage				
I-II	.177	0.56 (0.24-1.30)		
III	.315	0.69 (0.33-1.43)		
IV	**.066**	**1.76 (0.96-3.21)**		
Aerodigestive tumor	.663	1.14 (0.63-2.09)		
Cancer histology (SCC)	.470	1.30 (0.64-2.64)		
Prior Chemo/XRT	.509	1.21 (0.68-2.16)		
Preoperative Hgb (g/dL)	**<.001**	**0.63 (0.52-0.76)**	.002	0.61 (0.45-0.83)
Free flap type				
ALT	.470	1.23 (0.71-2.13)		
Forearm	**.004**	**0.36 (0.18-0.73)**		
Fibula	.801	0.92 (0.46-1.81)		
Other	**.006**	**2.62 (1.31-5.24)**		
Flap tissue (osseous)	.306	1.34 (0.77-2.35)		
Operative time (min)	**.001**	**1.003 (1.001-1.005)**	.036	1.003 (1.000-1.007)
Ischemia time (min)	**.016**	**1.008 (1.001-1.014)**		
EBL (mL)	**<.001**	**1.007 (1.005-1.010)**	<.001	1.006 (1.003-1.009)
IVF (mL)	**<.001**	**1.000 (1.000-1.000)**		

Note: All values with $P < .10$ upon univariate regression (bold) modeling were including in the initial multivariate model. Those variables with $P < .05$ on multivariate analysis using the backward Wald method were included in the final model and listed above.
Abbreviations: AJCC, American Joint Committee on Cancer; ALT, anterolateral thigh; BMI, body mass index; Chemo/XRT, chemotherapy and/or radiation therapy; CI, confidence interval; EBL, estimated blood loss; Hgb, hemoglobin; IVF, intravenous fluids; mCCI, modified Charlson Comorbidity Index; OR, odds ratio; SCC, squamous cell carcinoma.

3.3 | Binary logistic regressions of transfusion

Tables 3 and 4 summarize the univariate and multivariate binary logistic regressions of the predictive variables for intraoperative, postoperative, and overall perioperative transfusions. The final model of intraoperative transfusion included sarcopenia ($P = .023$, OR [95% CI] = 3.34 [1.18-9.46]), preoperative Hgb ($P = .002$, OR = 0.61 [0.45-0.83]), operative time ($P = .036$, OR = 1.003 [1.000-1.007]), and EBL ($P < .001$, OR = 1.006 [1.003-1.009]). Postoperative transfusion alone was predicted by preoperative Hgb ($P = .007$, OR = 0.72 [0.57-0.92]), osseous flap ($P = .036$, OR = 2.54 [1.06-6.06]), and CD ≥3 ($P < .001$, OR = 8.30 [3.35-20.56]). The final regression model of receiving a 30-day perioperative transfusion including all pre-, intra-, and postoperative variables demonstrated sarcopenia ($P = .021$, OR = 2.83 [1.17-6.86]), preoperative Hgb ($P < .001$, OR = 0.059 [0.46-0.76]), operative time ($P = .008$, OR = 1.004 [1.001-1.006]), and CD ≥ 3 ($P = .018$, OR 2.98 [1.20-7.39]) as independent predictive factors.

4 | DISCUSSION

Herein we identified those patients and characteristics most likely to predict transfusion in HNCFFR. This population is at highest risk of requiring transfusion among head and neck surgeries due to the magnitude of resection and reconstruction required. After separation of transfusions into intra-, post-, and perioperative transfusions, sarcopenia remained an independent predictor of intraoperative and perioperative transfusions in this extensive analysis of pre-, intra-, and

TABLE 4 Binary logistic regression of postoperative and perioperative transfusion requirements

	Postoperative				Perioperative			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Sex (male)	.350	0.75 (0.41-1.37)			.163	0.68 (0.39-1.17)		
Race (white)	**.038**	**0.303 (0.10-0.94)**			.256	0.51 (0.16-1.62)		
Age (y)	.700	1.00 (0.98-1.03)			.187	1.01 (0.99-1.03)		
BMI (kg/m^2)	**.036**	**0.95 (0.91-0.99)**			**.007**	**0.95 (0.91-0.99)**		
Smoking	.374	1.34 (0.70-2.57)			.344	1.32 (0.75-2.32)		
Alcohol	**.014**	**2.10 (1.16-3.79)**			.051	1.73 (1.00-2.99)		
Sarcopenia	**.025**	**2.03 (1.10-3.76)**			**<.001**	**3.72 (2.00-6.90)**	.021	2.83 (1.17-6.86)
mCCI	**.001**	**1.31 (1.11-1.54)**			**<.001**	**1.36 (1.14-1.61)**		
AJCC stage IV	.080	1.78 (0.93-3.83)			**.024**	**1.90 (1.09-3.32)**		
Aerodigestive tumor	.629	1.17 (0.62-2.23)			.596	1.17 (0.66-2.06)		
Histology (SCC)	.342	0.71 (0.36-1.43)			.924	0.97 (0.51-1.86)		
Prior Chemo/XRT	.892	0.96 (0.52-1.77)			.409	1.26 (.73-2.18)		
Preop Hgb (g/dL)	**.002**	**0.76 (0.65-0.90)**	.007	0.72 (0.57-0.92)	**<.001**	**0.63 (0.52-0.75)**	<.001	0.59 (0.46-0.76)
Free flap type								
ALT	.611	1.16 (0.65-2.09)			.502	1.20 (0.71-2.03)		
Forearm	**.001**	**0.24 (0.10-0.56)**			**<.001**	**0.32 (0.17-0.60)**		
Fibula	.146	1.65 (0.84-3.26)			.440	1.29 (0.68-2.45)		
Other	.058	1.99 (0.98-4.04)			**.010**	**2.54 (1.25-5.16)**		
Flap tissue (osseous)	**.005**	**2.32 (1.29-4.15)**	.036	2.54 (1.06-6.06)	**.025**	**1.86 (1.08-3.19)**		
Operative time (min)	**.008**	**1.002 (1.001-1.004)**			**.001**	**1.003 (1.001-1.004)**	.008	1.004 (1.001-1.006)
Ischemia time (min)	**.010**	**1.009 (1.02-1.015)**			**.014**	**1.008 (1.002-1.014)**		
EBL (mL)	**.004**	**1.001 (1.000-1.002)**			**<.001**	**1.007 (1.005-1.009)**		
IVF (mL)	.442	1.000 (1.000-1.000)			**.015**	**1.000 (1.000-1.000)**		
Intraoperative transfusion	**<.001**	**3.52 (1.94-6.37)**						
CD ≥ 3	**<.001**	**6.86 (3.56-13.25)**	<.001	8.30 (3.35-20.56)	**<.001**	**3.48 (1.83-6.62)**	.018	2.98 (1.20-7.39)

Note: A total of n = 66 thirty-day postoperative and n = 110 perioperative (intra- and postoperative) blood transfusions occurred. All values with $P < .05$ upon univariate regression (bold) modeling were including in the initial multivariate model. Those variables with $P < .05$ on multivariate analysis using the backward Wald method were included in the final model and listed above.

Abbreviations: AJCC, American Joint Committee on Cancer; ALT, anterolateral thigh; BMI, body mass index; CD, Clavien-Dindo score; Chemo/XRT, chemotherapy and/or radiation therapy; CI, confidence interval; EBL, estimated blood loss; Hgb, hemoglobin; IVF, intravenous fluids; mCCI, modified Charlson Comorbidity Index; OR, odds ratio; SCC, squamous cell carcinoma.

postoperative variables. To the best of our knowledge, our study is the first to separate transfusions into these different time frames and analyze them separately.

CT-quantified SMM has remained a reliable, anthropometric measurement to identify patients at risk for postoperative complications and mortality across HNC and/or FFR patients.[20-27] Given that CT imaging is obtained in almost all HNCFFR cases, it would be prudent to extract as much information as possible from these diagnostic tests. Optimally, SMI measurements would be combined with clinical testing of strength and functionality to fit the most recent iteration of sarcopenia.[10] However, radiologically determined sarcopenia alone harbors substantial evidence of its negative effect in medical comorbidity and mortality.[11-27] To the best our knowledge, investigations combining SMM and strength/function measurements have not yet been performed in HNCFFR to suggest any improved postoperative prognostication.

Although SMI and BMI are correlated,[20,27,38] BMI does not differentiate between adipose or muscle composition. For instance, patients can have low SMI yet have normal or obese BMI. The converse can also be true with low BMI but normal SMI. BMI has not demonstrated any significant effect on 30-day postoperative complications, transfusion rates, or mortality in HNCFFR.[39,40] However, SMI has been compellingly linked to a number of postoperative complications and survival in HNCFFR.[20-25,27] This study supplements those prior findings by demonstrating SMI as a more robust predictor of transfusions in HNCFFR than BMI. Therefore, significant evidence suggests the superiority of SMI to BMI in preoperative risk stratification in HNCFFR, which has been previously validated in lung and gastrointestinal malignancies.[41]

The reported rates of sarcopenia in HNC range from 28.3% to 77%.[20-25] This variance may be attributed to the discrepancy of SMI cutoff values, the specific skeletal muscles measured, whether males and females had separate cutoff criteria, and the study group tumor characteristics. The sarcopenia cutoff values in this investigation were based on the 5th percentile of SMIs in a healthy, adult, Caucasian population.[38] Cutoffs for other HNC investigations[21-25] were established from a study of chemotherapy dose-limited toxicity in HNC[42] or other cancer studies that do not involve HNC.[41,43] While other studies have analyzed sarcopenia prevalence at one head and neck tumor location,[21-25] this investigation included malignancies of all head and neck subsites rather than one specific region. Some studies have used cervical muscle instead of abdominal muscle to measure SMI.[22,26] These incongruencies may account for the variance of reported HNC sarcopenia rates. Large population-based studies are needed to adequately determine SMI cutoff values to promote homogeneity in definitions and reported incidences.

Regardless of variable prevalence, sarcopenia in the HNC population is considerable. Its occurrence and etiology are similar to other advanced malignancies that impair nutritional and/or functional status.[11,12,44,45] Malnutrition in HNC is partially attributed to the high rates of alcohol abuse. Furthermore, advanced aerodigestive malignancy prevents the ingestion of food due to pain, physical obstruction, or functional dysphagia and aspiration. Cancer cachexia plays a prominent role by upregulating degradation and impairing anabolism of skeletal muscle.[46] Due to considerable rates of tobacco and ethanol use, HNC patients also have greater incidences of major comorbidities including COPD, CHF, CVA, PVD, and CAD. These diseases limit physical capacity to promote sedentary lifestyles and muscular atrophy.

Our study and prior literature have reported intraoperative and total perioperative transfusion rates in HNCFFR ranging 24.6% to 33.5% and 46.0% to 82.0%, respectively.[8,47-49] This high incidence is partly attributed to preoperative anemia frequently identified in HNC patients.[49-51] It is intuitive that certain comorbidities (e.g., renal failure), low Hgb, and more extensive resections or reconstructions with greater blood loss would elevate transfusion requirements, as identified in our and others' reports.[49,50,52] Including HNC patients undergoing free or pedicled flap reconstruction, Weber et al identified low preoperative Hgb, advanced T-stage, and FFR as factors conferring the highest risk of perioperative transfusion.[50] Shah et al, although without evaluation of blood loss, determined female sex, advanced T-stage, underweight BMI, low preoperative Hgb, and osseous flaps as predictors of intraoperative transfusion.[49] In a broader study on FFR, Kolbenschlag et al identified age > 60 years, myocutaneous flaps, low preoperative Hgb and platelets, and cardiac or renal insufficiency as predictors of intraoperative transfusion.[52] Only 5% of their 398 FFR involved the head/neck or trunk, however, and no records of EBL or change in Hgb were included. Our investigation identified similar results to these investigations on univariate analysis, but the inclusion of sarcopenia on multivariate regression failed to identify low BMI, advanced cancer stage, or flap type as independent predictors. This suggests preoperative sarcopenia may be a more powerful representation and predictor of the patient's response to their malignancy and surgery.

The exact etiology for increased transfusions in sarcopenia remains elusive. One explanation could be the smaller body volume reserve within sarcopenic patients, a phenomenon that has been observed in underweight patients.[40] However, BMI was insignificant after accounting for SMI in this study. We believe this can be attributed to the relatively higher vascular supply and density of skeletal muscle than adipose. Sarcopenic patients also have reduced SMM and capillary density, both which would diminish patient total blood volume and increase the relative detriment of blood loss.[28] Another argument for elevated transfusion is the extent of resection, evidenced by sarcopenic patients tending to have more advanced local disease, undergo more complex resections, and require reconstruction with flaps other than the smaller forearm free flaps.[20] With that speculation, the assumption would be that greater EBL would account for the need for transfusions, yet that was not observed in our results. There remains the possibility that EBL values were inaccurate as it is a crude approximation of volume, but the inaccuracy would arguably be distributed across patients equally. Another consideration is the physician's judgment for providing transfusion, as each anesthesiologist has their own tendencies regardless of guidelines. Regarding specifically postoperative transfusions, low Hgb and incurring a major postoperative complication are logical causes of requiring a transfusion, for

which sarcopenia was not an independent predictor. Despite an unclear cause, the link between sarcopenia and transfusion requirements has been similarly documented in other investigations.[30-33]

To mitigate the deleterious consequences of administering blood products, investigations have sought the use of more restrictive transfusion guidelines in otherwise asymptomatic patients. Studies in otolaryngology and other fields have not identified worse outcomes with more restrictive transfusion.[47,53-55] Investigations of these thresholds in sarcopenia patients may demonstrate different appropriate transfusion criteria.

Several implications exist for identifying preoperative sarcopenia in HNCFFR. As these patients are more likely to have transfusions, there is an expected increase in hospital cost and potential postoperative complications.[2,5-7] This should be discussed with the patient preoperatively and be considered in the setting of scarce blood product supply. Preoperative ABO cross-matching and blood product preparation should be performed. Special attention should be made to hemostasis and IVF administration to prevent dilution and unnecessary blood loss. Patients with sarcopenia should also have multimodal, preoperative nutrition and rehabilitation maximized in order to minimize the effects of sarcopenia and major surgery.[56,57]

Several limitations to this study exist. It is retrospective and therefore subject to bias of the medical documentation and interpretation. Due to limited recording, we did not include any preoperative nutrition or inflammatory laboratory values that have demonstrated a negative effect on surgical outcomes.[40,44,58-60] Our sample size is limited by patients with preoperative CT imaging of the abdomen, which generally are limited to those patients with positron emission tomography (PET) CT scans or CT angiograms. Furthermore, the CT scans must be of adequate quality to measure skeletal muscle (e.g., metallic screws in vertebrae that distort images). Utilizing cervical CT scans instead of abdominal CT scans to calculate SMI would increase the available population for sampling due to commonplace use in head and neck surgery. Calculating SMI using cervical skeletal muscle on head and neck CT imaging has been reported in several studies. These investigators estimated abdominal SMI using an equation that includes cervical skeletal muscle values and subsequently determined sarcopenia from those calculations.[22,23,25,26,42,61] Further investigations are required to define sarcopenia cutoff values using healthy, population-based, cervical SMI values rather than determining sarcopenia from multivariable extrapolation.

5 | CONCLUSIONS

Sarcopenia is associated with intraoperative and perioperative transfusions in HNCFFR and therefore may increase the risk of transfusion-related complications. These should be discussed with patients preoperatively and taken into consideration in settings of limited blood product availability.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Alexander Joseph Jones https://orcid.org/0000-0002-9219-285X
Mohamedkazim Alwani https://orcid.org/0000-0002-8311-4040
Leah J. Novinger https://orcid.org/0000-0002-9018-7838
Brady Jay Tucker https://orcid.org/0000-0002-4127-1689
Andrea Bonetto https://orcid.org/0000-0002-3235-1871
Jessica A. Yesensky https://orcid.org/0000-0002-1558-9693
Michael W. Sim https://orcid.org/0000-0001-6571-9452
Avinash V. Mantravadi https://orcid.org/0000-0002-7971-481X

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