Oral Oncology 99 (2019) 104467

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Development and validation of a nomogram incorporating selected systemic inflammation-based prognostic marker for complication prediction after vascularized fibula flap reconstruction

Zhongqi Liu[1], Haixuan Wu[1], Ning Liufu, Shi Cheng, Haoquan Huang, Chuwen Hu, Minghui Cao*

Department of Anesthesiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 510120 Guangzhou, PR China

ARTICLE INFO

Keywords:
The ANS
Nomogram
Postoperative complication
Vascularized fibula flap reconstruction

ABSTRACT

Objective: To develop and validate a nomogram incorporating systemic inflammatory markers (the Albumin/NLR Score [ANS]) to predict postoperative complications after vascularized fibula flap reconstruction.

Patients and methods: A total of 238 patients who underwent vascularized fibula flap reconstruction between March 2012 and December 2016 were collected as the primary cohort. Univariable and multivariable analysis were performed to identify independent risk factors for postoperative complications. Backward stepwise logistic regression analysis was then applied with and without the ANS; and nomograms were established based on these criteria. Independent validation of these nomograms was carried out in an independent validation cohort including 106 consecutive patients from December 2016 and January 2018.

Results: Radiotherapy history (odds ratio [*OR*] = 0.336; 95% *CI*, 0.157–0.717; $P = 0.005$), the ANS (*OR* = 0.248; 95% *CI*, 0.093–0.661; $P = 0.005$) and fluid infusion rate over 24 h (*OR* = 0.671; 95% *CI*, 0.479–0.94; $P = 0.02$) were identified as independent risk factors for postoperative complications. A higher C-index was found in both the primary (0.759; 95% *CI*, 0.719–0.739) and validation cohort (0.704; 95% *CI*, 0.613–0.659) for the nomogram incorporating the ANS, and NRI was 0.496 (95% *CI*, 0.072–0.920; $P = 0.022$) comparing of these nomograms. Furthermore, a wider threshold probability (0.2–0.9) and superior clinical value were observed in the nomogram incorporating the ANS on the decision curve.

Conclusion: The ANS was an independent risk factor for postoperative complications associated with vascularized fibula flap reconstruction. The nomogram incorporating the ANS was established with better accuracy and showed more potential clinical benefit for the estimation of postoperative complications.

Introduction

Vascularized fibula flap reconstruction has been the major standard treatment for mandibular defects caused by tumor resection and osteonecrosis [1]. Although fibula flap transfer enables the restoration of jaw function and facial aesthetics, lengthy complicated procedure should be performed to achieve the ultimate aim of prosthodontic rehabilitation, which is often associated with complications, high morbidity and increased costs. Therefore, Identification of risk factors for postoperative complications is of great clinical value. And further predicting the likelihood of postoperative complications would significantly facilitate the personalized treatment strategies optimally suited for each patient.

To date, great efforts have been made to identify risk factors for flap complications. Apart from surgical manipulation, the importance of perioperative evaluation and management in postoperative complication has been identified. However, there are considerable discrepancies in the previously reported findings. Some studies noted a significant association between radiotherapy history and the incidence of perioperative complications [2,3], while the others presented totally

Abbreviations: ANS, Albumin/NLR Score; OR, Odds ratio; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; mGPS, Modified Glasgow prognostic score; IRB, Institutional Review Board; ASA, American Society of Anesthesiologists; CHD, Coronary heart disease; CRP, C-reactive protein; Alb, Albumin; ROC, Receiver operating characteristic; Hgb, Hemoglobin; Hct, Hematocrit; RBC, Red blood cell; NRI, Net reclassification improvement; DCA, Decision curve analysis; NETs, Neutrophil extracellular traps

* Corresponding author at: Department of Anesthesiology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, 107 Yanjiang West Road, Guangzhou 510120, PR China.

E-mail address: caomh@mail.sysu.edu.cn (M. Cao).

[1] Co-first authors.

https://doi.org/10.1016/j.oraloncology.2019.104467
Received 3 August 2019; Received in revised form 23 September 2019; Accepted 22 October 2019
Available online 01 November 2019

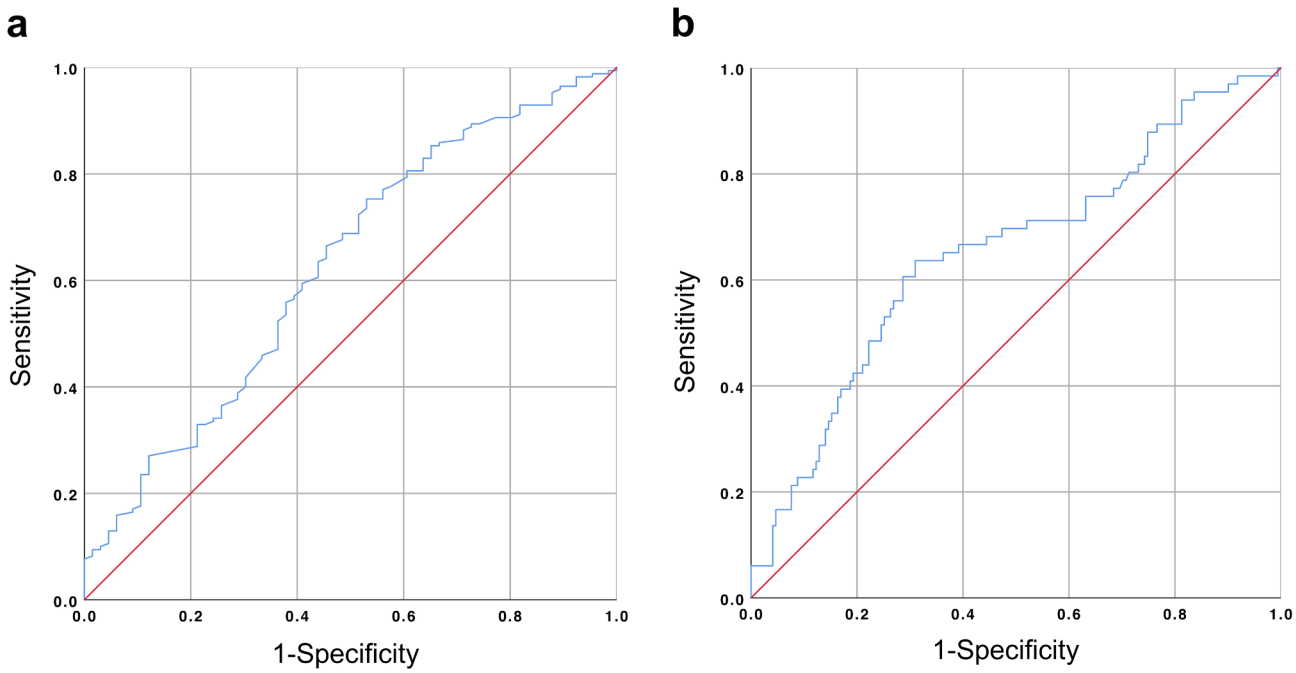

Fig. 1. ROC Curve of Preoperative Alb and the NLR in the Primary Cohort: (a) ROC curve of preoperative Alb (blue line) in the primary cohort; (b) ROC curve of the preoperative NLR (blue line) in the primary cohort. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

opposite findings [4,5]. Thus, although these studies provide insights into risk factors of perioperative complications to a certain extent, translating these observations into practical measurable surgical outcomes and providing patient care for individual patients remains challenging.

Over the last decade, there was good consistent evidence that some markers of systemic inflammatory response, like C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), are associated with poor cancer-specific survival independent of tumor stage [6–8] and are clinically useful to predict the risk of complications in patients undergoing surgery for a variety of common solid tumors [9–11]. In addition to several ratios based on circulating blood cell counts mentioned above, some inflammation-based score system has been established to refine risk prediction for specific patients. Modified Glasgow prognostic score (mGPS), which combines both the CRP and albumin, was most commonly utilized. Recent study demonstrate that compared with CRP, the NLR may have better sensitivity and specificity in predicting postoperative complications [12]. On further investigation, the ANS, which combines NLR and albumin, has shown prognostic value for oral and gastric cancer patients [13,14]. However, notably, there is a dearth of data evaluating the predictive ability of the ANS for the risk of complications after mandibulofacial reconstruction with a fibula flap, which jeopardizes the accuracy of predicting the likelihood of complications in patients. To realize the goal of predicting personalized surgical outcomes and performing preoperative risk stratification, a comprehensive and applicable tool that incorporates markers that span different aspects is urgently needed.

Nomogram is a statistical tool that use two or more known variables to calculate the probability of a particular outcome for an individual patient [15]. This method demonstrated advantages over traditional methods to predict long-term outcomes in a variety of cancer types [16,17] and have been gradually adopted in an extensive array of applications including cancer, surgery and other diseases [18,19]. Hence, the present study aimed to investigate the predictive value of the ANS and to construct a nomogram based on perioperative variables to predict the likelihood of postoperative complications after vascularized fibula flap reconstruction.

Patients and methods

Patients

The study protocol was approved by the Institutional Review Board (IRB) of Sun Yat-Sen Memorial Hospital. The medical records of patients who underwent fibula free flap interventions for reconstruction of defects in the mandibulofacial region at Sun Yat-sen Memorial Hospital between March 2012 and December 2016 were collected and categorized as the primary cohort. Patients who underwent the same medical treatment between December 2016 and January 2018 were collected and categorized as the validation cohort. Death cases or cases with missing data for demographic characteristics, preoperative examinations, surgical and fluid variables were excluded from the analysis.

Data collection

Demographic characteristics, including sex, age, weight, American Society of Anesthesiologists (ASA) status, smoking status, radiotherapy history, comorbidities (hypertension, diabetes, stroke, coronary heart disease [CHD], cirrhosis and others) and the reasons for the flap (benign or malignant tumor, osteoradionecrosis) were retrieved from patients' medical records. Preoperative laboratory examination data within seven days prior to operation including hemoglobin, serum CRP, albumin (Alb) and differential blood cell counts were recorded, and the NLR value was calculated. The cut-off points for albumin and NLR were 37.150 g/L and 2.723 respectively (defined by receiver operating characteristic [ROC] curve analysis in Fig. 1). Values below the cut-off value for albumin and over the cut-off value for NLR were given 1 point each, which providing a possible ANS score ranging from 0 to 2. Surgical variables included intraoperative blood loss, duration of surgery, vasopressor administration and intraoperative blood transfusion. The decision to use vasopressors (i.e. norepinephrine, dopamine or ephedrine) was made by the anesthesia team on a case-by-case basis. A blood transfusion was required when the hemoglobin (Hgb) level was

lower than 70 g/L or the hematocrit (Hct) was lower than 25% in patients with uncompromised function (cardiac or pulmonary). In hemodynamically compromised patients, a blood transfusion was recommended when the Hct was lower than 25% for patients younger than 60 years or when the Hct was lower than 30% for patients older than 60 years. Fluid variables included the type, volume and rate of intraoperative fluid infusion and fluid infusion over 24 h (crystalloid, colloid and total). The intraoperative fluid infusion rate and infusion rate over 24 h were standardized to the patient's body weight (mL/kg/hr). Intraoperative fluid infusions were administered at the discretion of the anesthesiologists on the basis of intra-arterial blood pressure monitoring, stroke volume variation, and the patient's urine output. The rate of postoperative fluid infusions was titrated by the surgical team, considering the patient's heart rate, blood pressure, and urine output. The postoperative complications were divided into surgical and medical complications. Surgical complications included partial and total flap loss; bleeding; thromboembolism of flap; fistula formation; wound dehiscence; and surgical site infections. Medical complications included pneumonia; pneumothorax; acute coronary syndrome; heart failure; stroke; and renal failure [20].

Univariate and multivariate comparison among groups and cohorts

The univariable association of baseline demographic data, preoperative laboratory examination parameters, surgical variables, fluid variables and postoperative complications between the primary and validation cohorts were assessed. Patients suffered from both surgery and medical postoperative complications were included into complication-positive group and those who didn't were included into complication-negative group. Univariable and multivariable comparisons between the complication-positive and complication-negative groups in the primary cohort were then performed to identify risk factors for postoperative complications. The features for multivariable comparison were selected by collinearity diagnostics.

Predictive value of preoperative systemic inflammation

After collinearity diagnostics, candidate predictors including age, ASA status, smoking status, total comorbidity, radiotherapy history, vasopressor administration, intraoperative red blood cell (RBC) transfusion, intraoperative infusion rate and fluid infusion rate over 24 h were identified. To determine the predictive value of preoperative systemic inflammation, multivariable backward stepwise logistic regression analyses begining with the candidate predictors with and without the ANS were applied to build predictive models. The two models were then compared in accuracy (C-index, calibration curve and net reclassification improvement [NRI]) and potential clinical benefit (decision curve analysis [DCA]).

Development of nomogram

To establish predictive models, backward stepwise logistic regression analysis was applied with and without the ANS as mentioned above in the primary cohort using the likelihood ratio test with Akaike's information criterion as the stopping rule [21,22]. To provide a quantitative tool to predict the individual probability of complications, we built nomograms based on these predictive models.

Validation of the nomograms

Calibration curves were plotted to assess the performance of the two nomograms for the occurrence of complications. The nomograms were subjected to bootstrapping validation (1000 bootstrap resamples) to calculate a relatively corrected C-index in the primary cohort. The logistic regression models from the primary cohort were then applied to all the patients in the validation cohort, and the total points for each patient was calculated. Logistic regression in the validation cohort was then performed using the total points as a factor. Finally, the C-index and calibration curve were derived on the basis of the regression analyses in both the primary and the validation cohort.

Clinical benefit evaluation

The DCA was conducted to determine the clinical usefulness of the nomograms for predicting complications by quantifying the standardized net benefits at different threshold probabilities in the validation dataset [23]. The decision curves were plotted for nomograms with and without the ANS.

Statistical analysis

Univariable and multivariable analysis was performed with IBM SPSS software (version 25.0; SPSS Inc, Chicago, IL). Continuous variables were assessed by the *t*-test or the Mann-Whitney *U* test according to normality for variables. Categorical variables were assessed by the chi-square test or Fisher exact test according to the frequencies of variables. Development, validation of nomograms and DCA were performed with R software (version 3.0.1; http://www.Rproject.org). The packages in R that were used in this study were "rms" and "rmda". Differences with $P < 0.05$ were considered statistically significant. Continuous variables are presented as the mean ± standard deviation (S.D.). Categorical variables are presented as the No. (%)

Results

Patients and clinical characteristics

A total of 358 patients who underwent fibula free flap interventions from January 2012 to January 2018 were originally collected. One patient was excluded due to death after operation and thirteen patients were excluded due to lack of information. Finally, 344 patients were included in the study. 238 patients were assigned to the primary cohort and 106 patients were assigned to the validation cohort. The total flap survival rate in this study was 96.5% (332/344), with 12 patients required secondary operation for flap re-transplant due to total flap loss. The postoperative complications occurred in 97 patients (28.2%), including bleeding (n = 10), thromboembolism of flap (n = 15), flap loss (partial, n = 19; total, n = 12), fistula formation (n = 21), wound dehiscence (n = 14), surgical site infections (n = 8), pneumonia (n = 7), pneumothorax (n = 3), acute coronary syndrome (n = 2), heart failure (n = 2), stroke (n = 2) and renal failure (n = 1). Among these 97 patients, 51 (14.8%) underwent a secondary operation due to bleeding, thromboembolism of flap or flap loss. Patient characteristics in the primary and validation cohorts are given in Table 1. No significant difference was found between these two cohorts.

Univariate and multivariate analysis in the primary cohort

The univariate and multivariate comparison between the complication-positive and complication-negative groups in the primary cohort is shown in Table 2. Demographic characteristics included the ASA status, radiotherapy history, reasons for the flap; preoperative laboratory examination parameters included Hgb, Alb, neutrophil count, lymphocyte count, CRP level, the NLR, and the ANS; surgical and fluid variables included intraoperative RBC transfusion and the amount of fluid infusion over 24 h were significantly different between the complication-positive and complication-negative groups (Table 2). In multivariate analysis, radiotherapy history, the ANS and fluid infusion rate over 24 h were identified as independent risk features for the occurrence of complications after vascularized fibula flap reconstruction (Table 2).

Table 1
Patient characteristics in the primary and validation cohorts.

	Primary Cohort (n = 238)	Validation Cohort (n = 106)	p
Age, No. (%), yr			
< 45	65 (27.3)	32 (30.2)	0.725
45–65	132 (55.5)	59 (55.7)	
> 65	41 (17.2)	15 (14.2)	
Male, No. (%)	159 (66.8)	77 (72.6)	0.282
Weight, mean (SD), Kg	58.255 (0.700)	57.983 (0.970)	0.825
ASA Status, No. (%)			
1 or 2	135 (56.7)	48 (45.3)	0.05
3	103 (43.3)	58 (54.7)	
Smoking Status, No. (%)	67 (28.2)	30 (28.3)	0.977
Comorbidities, No. (%)			
Hypertension	34 (16.7)	13 (12.3)	0.614
Diabetes Mellitus	13 (5.5)	6 (5.6)	0.941
Stroke	3 (1.3)	0 (0.0)	0.555
Coronary Heart Disease	2 (0.8)	1 (0.9)	1
Cirrhosis	2 (0.8)	0 (0.0)	1
Others	3 (1.3)	0 (0.0)	0.555
Total	47 (19.7)	16 (15.1)	0.776
Radiotherapy History, No. (%)	57 (23.9)	24 (22.6)	0.776
Reason for Flap, No. (%)			
Osteoradionecrosis	58 (24.4)	27 (25.5)	0.827
Tumor	173 (72.7)	73 (68.9)	0.468
Preoperative			
Hemoglobin, mean (SD), g/L	129.945 (1.167)	131.029 (1.568)	0.595
Albumin, mean (SD), g/L	39.301 (0.318)	38.834 (0.419)	0.401
Neutrophils, mean (SD), $\times 10^9$/L	4.620 (0.176)	4.586 (0.152)	0.904
Lymphocytes, mean (SD), $\times 10^9$/L	1.778 (0.042)	1.852 (0.070)	0.345
C-Reactive Protein, mean (SD), mg/L	15.508 (2.059)	10.413 (1.945)	#0.221
NLR, mean (SD)	3.152 (0.209)	2.866 (0.152)	0.387
ANS = 0, No. (%)	110 (46.2)	44 (41.5)	0.31
ANS = 1, No. (%)	79 (33.2)	43 (40.6)	
ANS = 2, No. (%)	47 (19.7)	16 (15.1)	
Blood Loss, mean (SD), ml	498.228 (18.685)	450.472 (23.928)	0.139
Duration of Surgery, mean (SD), min	471.878 (11.377)	501.557 (16.706)	0.146
Intraoperative, mean (SD), ml			
Crystalloid Infusion	2711.555 (60.563)	2823.113 (87.837)	0.303
Colloid Infusion	954.622 (27.265)	929.245 (44.901)	0.617
Fluid Infusion	3661.555 (74.055)	3751.415 (107.761)	0.497
Intraoperative Fluid Infusion Rate, mean (SD), ml/ (kg × h)	9.171 (0.332)	8.455 (0.270)	0.177
Intraoperative RBC Transfusion, mean (SD), u	1.674 (0.149)	1.642 (0.224)	0.903
Intraoperative FFP Transfusion, mean (SD), ml	155.462 (16.257)	166.981 (23.705)	0.692
Intraoperative Urine, mean (SD), ml	1075.365 (47.181)	1086.762 (65.081)	0.891
24 h Postoperatively, mean (SD), ml			
Crystalloid Infusion	3928.151 (74.437)	3704.245 (95.579)	0.082
Colloid Infusion	1005.462 (36.301)	1127.830 (46.904)	0.052
Fluid Infusion	5064.706 (86.703)	4827.359 (108.114)	0.111
Fluid Infusion Rate over 24 h, mean (SD), ml/ (kg × h)	3.706 (0.072)	3.539 (0.088)	0.178
Vasopressor Administration, No. (%)	41 (17.2)	20 (18.9)	0.656
Complications, No. (%)	67 (28.2)	30 (28.3)	0.977

Abbreviations: ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio; ANS, albumin/NLR score.
The *P* value is derived from the univariable association analyses between each of the demographic variables between the primary and validation cohorts.
# indicates that the Mann-Whitney *U* test was utilized.

Feature selection and nomogram development

Backward stepwise logistic regression analysis identified the ASA status, smoking status, radiotherapy history, intraoperative RBC transfusion and fluid infusion rate over 24 h as independent predictors for the occurrence of postoperative complication when the ANS was not included in the analysis (Table 3); while radiotherapy history, intraoperative RBC transfusion, fluid infusion rate over 24 h, vasopressor administration and the ANS were distinguished in backward stepwise logistic regression analysis as independent predictors for postoperative complication when the ANS was included in backward stepwise logistic regression analysis (Table 3). Models that incorporated the above independent predictors were developed and presented as nomograms (Fig. 2).

Validation of the nomograms

In the primary cohort, the C-index of the predictive nomogram without the ANS (Model 1) was 0.729 (95% *CI*, 0.719–0.739). In the validation cohort, the C-index was 0.636 (95% *CI*, 0.613–0.659). Higher C-index was observed in both the primary cohort (0.759; 95% *CI*, 0.750–0.768) and validation cohort (0.704; 95% *CI*, 0.679–0.729) for the nomogram incorporating the ANS in the backward stepwise logistic regression analysis (Model 2, Table 3). The calibration curves also showed that the prediction by Model 2 was in better accordance with the observed occurrence of complications than that of the Model 1 (Fig. 3).

In addition, the NRI compared between these 2 models was 0.496 (95% *CI*, 0.072–0.920; $P = 0.022$). The NRI for events showed no difference between these 2 models (0.071; 95% *CI*, −0.298–0.441; $P = 0.705$), while the NRI for nonevents was 0.425, and a significant difference was observed (95% *CI*, 0.217–0.632; $P < 0.001$).

Table 2
Univariate and Multivariate Comparisons between the Complication-Positive and Complication-Negative Groups in the Primary Cohort.

	Complication-Positive Group (n = 67)	Complication-Negative Group (n = 171)	univariate	Multivariate	OR (95% CI)
Age, No. (%), yr					
< 45	17 (25.4)	48 (28.1)	0.825	0.403	1.682 (0.498 to 5.680)
45–65	37 (55.2)	95 (55.6)		0.877	1.081 (0.404 to 2.889)
> 65	13 (19.4)	28 (16.4)			
Male, No. (%)	45 (67.2)	114 (66.7)	0.942		
Weight, mean (SD), Kg	57.246 (1.359)	58.653 (0.816)	0.366		
ASA Status, No. (%)					
1 or 2	31 (46.3)	104 (60.8)	0.042	0.217	0.640 (0.315 to 1.301)
3	36 (53.7)	67 (39.2)			
Smoking Status, No. (%)	24 (35.8)	43 (25.1)	0.1	0.317	0.688 (0.331 to 1.430)
Comorbidities, No. (%)					
Hypertension	10 (14.9)	24 (14.0)	0.86		
Diabetes Mellitus	5 (7.5)	8 (4.7)	0.395		
Stroke	0 (0.0)	3 (1.8)	0.561		
Coronary Heart Disease	1 (1.5)	1 (0.6)	0.485		
Cirrhosis	1 (1.5)	1 (0.6)	0.485		
Others	2 (3.0)	1 (0.6)	0.192		
Total	14 (20.9)	33 (19.3)	0.781	0.884	0.935 (0.378 to 2.311)
Radiotherapy History, No. (%)	30 (44.8)	27 (15.8)	< 0.001	0.005	0.336 (0.157 to 0.717)
Reason for Flap, No. (%)					
Osteoradionecrosis	27 (40.3)	31 (18.1)	< 0.001		
Tumor	36 (53.7)	137 (80.1)	< 0.001		
Preoperative					
Hemoglobin, mean (SD), g/L	125.636 (2.192)	131.627 (1.361)	0.021		
Albumin, mean (SD), g/L	37.655 (0.620)	39.940 (0.359)	0.001		
Neutrophils, mean (SD), $\times 10^9$/L	5.539 (0.532)	4.265 (0.123)	#0.046		
Lymphocytes, mean (SD), $\times 10^9$/L	1.648 (0.093)	1.828 (0.046)	#0.021		
C-Reactive Protein, mean (SD), mg/L	23.339 (4.562)	12.441 (2.205)	# < 0.001		
NLR, mean (SD)	4.305 (0.635)	2.706 (0.143)	# < 0.001		
ANS = 0, No. (%)	16 (23.9)	94 (55.0)	< 0.001	0.005	0.248 (0.093 to 0.661)
ANS = 1, No. (%)	27 (40.3)	52 (30.4)		0.394	0.685 (0.287 to 1.634)
ANS = 2, No. (%)	23 (34.3)	27 (15.8)			
Blood Loss, mean (SD), ml	500.448 (34.997)	497.353 (22.162)	0.941		
Duration of Surgery, mean (SD), min	494.478 (22.659)	462.971 (13.089)	0.213		
Intraoperative, mean (SD), ml					
Crystalloid Infusion	2559.702 (120.160)	2771.053 (69.618)	0.117		
Colloid Infusion	960.448 (51.860)	952.339 (32.143)	0.894		
Fluid Infusion	3520.149 (150.497)	3716.959 (84.450)	0.233		
Intraoperative Fluid Infusion Rate, mean (SD), ml/(kg × h)	8.564 (0.544)	9.412 (0.410)	0.25	0.588	0.979 (0.905 to 1.058)
Intraoperative RBC Transfusion, mean (SD), u	2.388 (0.329)	1.395 (0.159)	#0.004	0.084	1.144 (0.982 to 1.334)
Intraoperative FFP Transfusion, mean (SD), ml	204.478 (36.492)	136.257 (17.394)	0.059		
Intraoperative Urine, mean (SD), ml	1267.692 (115.808)	1000.952 (46.707)	#0.099		
24 h Postoperatively, mean (SD), ml					
Crystalloid Infusion	3723.881 (144.972)	4008.187 (86.141)	0.086		
Colloid Infusion	968.657 (63.542)	1019.883 (44.027)	0.527		
Fluid Infusion	4772.388 (163.960)	5179.240 (101.109)	0.035		
Fluid Infusion Rate over 24 h,mean (SD), ml/(kg × h)	3.557 (0.131)	3.765 (0.087)	0.197	0.02	0.671 (0.479 to 0.940)
Vasopressor Administration, No. (%)	14 (20.9)	27 (15.8)	0.348	0.139	0.531 (0.229 to 1.227)

Abbreviations: ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio; ANS, albumin/NLR score.
Variables in the multivariable analysis were selected by collinearity diagnostics.
# indicates that the Mann-Whitney *U* test was utilized.

Clinical benefit evaluation

The DCA was presented in Fig. 4. Threshold probability is where the expected benefit of treatment is equal to the expected benefit of avoiding treatment. And patients would opt for treatment if their probability was higher than the threshold probability. The decision curve showed that if the threshold probability of a patient or doctor was set between 20% and 50%, the benefit of using Model 1 (nomogram without the ANS) was beyond both green line (treat-all scheme) and black line (treat-none scheme). However, the threshold probability could be set between 20% and almost 90% when the benefit of using Model 2 (nomogram incorporating the ANS) was more than either the treat-all or treat-none scheme. In addition, a higher net benefit of the Model 2 was also observed, as shown in Fig. 4.

Table 3
Risk factors for postoperative complication derived from backward stepwise logistic regression analysis.

		Model 1				Model 2			
		P	OR	95% CI of OR		P	OR	95% CI of OR	
ASA Status		0.101	0.591	0.315	1.109	NA	NA	NA	NA
Smoking Status		0.142	0.608	0.313	1.181	NA	NA	NA	NA
Radiotherapy History		0	0.249	0.124	0.497	0.004	0.337	0.163	0.701
Intraoperative RBC Transfusion		0.034	1.155	1.011	1.318	0.038	1.157	1.008	1.327
Fluid Infusion Rate over 24 h		0.014	0.685	0.507	0.925	0.011	0.668	0.491	0.91
Vasopressor Administration		NA	NA	NA	NA	0.136	0.538	0.238	1.216
ANS		NA	NA	NA	NA	0.004			
ANS = 0						0.002	0.255	0.108	0.605
ANS = 1						0.377	0.694	0.308	1.561
Intercept		0.014	6.244			0.008	9.531		
C-index	primary		0.729	0.719	0.739		0.759	0.750	0.768
	validation		0.636	0.613	0.659		0.704	0.679	0.729

Abbreviations: ASA, American Society of Anesthesiologists; ANS, albumin/NLR score.
Model 1 was established without the inclusion of the ANS in the backward stepwise logistic regression analysis. The risk factors in Model 1 included the ASA, smoking status, radiotherapy history, intraoperative RBC transfusion and fluid infusion rate over 24 h. The C-index of Model 1 was 0.729 and 0.636 in the primary and validation cohort.
Model 2 was established with the inclusion of the ANS into the analysis, which included radiotherapy history, intraoperative RBC transfusion, fluid infusion rate over 24 h, vasopressor administration and the ANS. The C-index of Model 1 was 0.759 and 0.704 in the primary and validation cohort.

Discussion

In the present analysis, we identified that the ANS as an independent risk factor for postoperative complications after mandibulofacial defect reconstruction with a fibula free flap. In addition, this study further developed and validated a prognostic nomogram incorporating the ANS and other clinical risk factors to predict postoperative complications. The proposed nomogram could serve as an easy-to-use tool to permit more accurate risk stratification for individual patients.

Previous studies have shown that several blood cell-based prognostic biomarkers related to systemic inflammation are predictive of complications after major surgery such as the NLR [9,24]. However, there is limited evidence in the predictive value of systemic inflammation in flap transplant surgery. In the present study, the relationship between ANS and complications after mandibulofacial defect reconstruction with a fibula free flap was identified. The NLR is a classic biomarker for systemic inflammation and is based on the ratio of circulating neutrophils and lymphocytes, which can be calculated easily by routine blood tests without extra expenses; while Alb is a negative acute phase protein that is influenced by inflammation and other noninflammatory reasons such as malnutrition, acute stress, and increased age [25–27]. Therefore, we sellected the ANS, which represents the inflammation responses of different systems, the myeloid/lymphoid tissue and liver, to increase the predictive value of the nomogram for predicting postoperative complications after mandibulofacial reconstruction surgery with a fibula flap.

The ANS before surgery was proven to be an independent risk factor for postoperative complications in our study. In addition, integration of the ANS into the backward stepwise logistic regression analysis could significantly improve the performance of the nomogram in predicting the likelihood of complications after mandibulofacial reconstruction surgery. Previous studies have indicated that systemic inflammation may influence wound healing progress and the incidence of postoperative infection [28]. However, there is limited evidence on how the ANS influences flap survival after flap transplant surgery. It is known that coagulation plays a crucial role in flap survival [29]. Hence, the close relationship between inflammation and coagulation dysfunction may partially explain the results in the present study [30,31]. It has been proposed that neutrophil extracellular traps (NETs) are released from stimulated neutrophils in a process known as NETosis [32]. NETs are highly proinflammatory and prothrombotic fibers that can entrap leukocytes and propagate thrombosis [32,33]. On the other hand, low serum Alb levels were ranked the first regarding their predictive value for postoperative complications in the National Veterans Association Surgical Risk Study [34]. Some investigators have shown that patients with hypoalbuminemia are susceptible to infection and prone to sepsis [26,35]. In a population-based prospective cohort study, low serum Alb

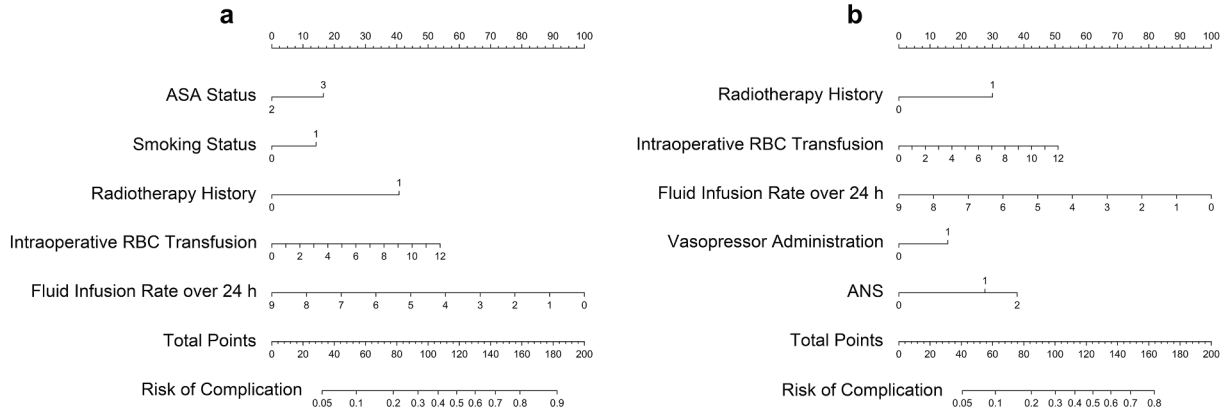

Fig. 2. Nomograms derived from backward stepwise logistic regression analyses. (a) The nomogram without the ANS in backward stepwise logistic regression analysis; (b) The nomogram incorporating the ANS.

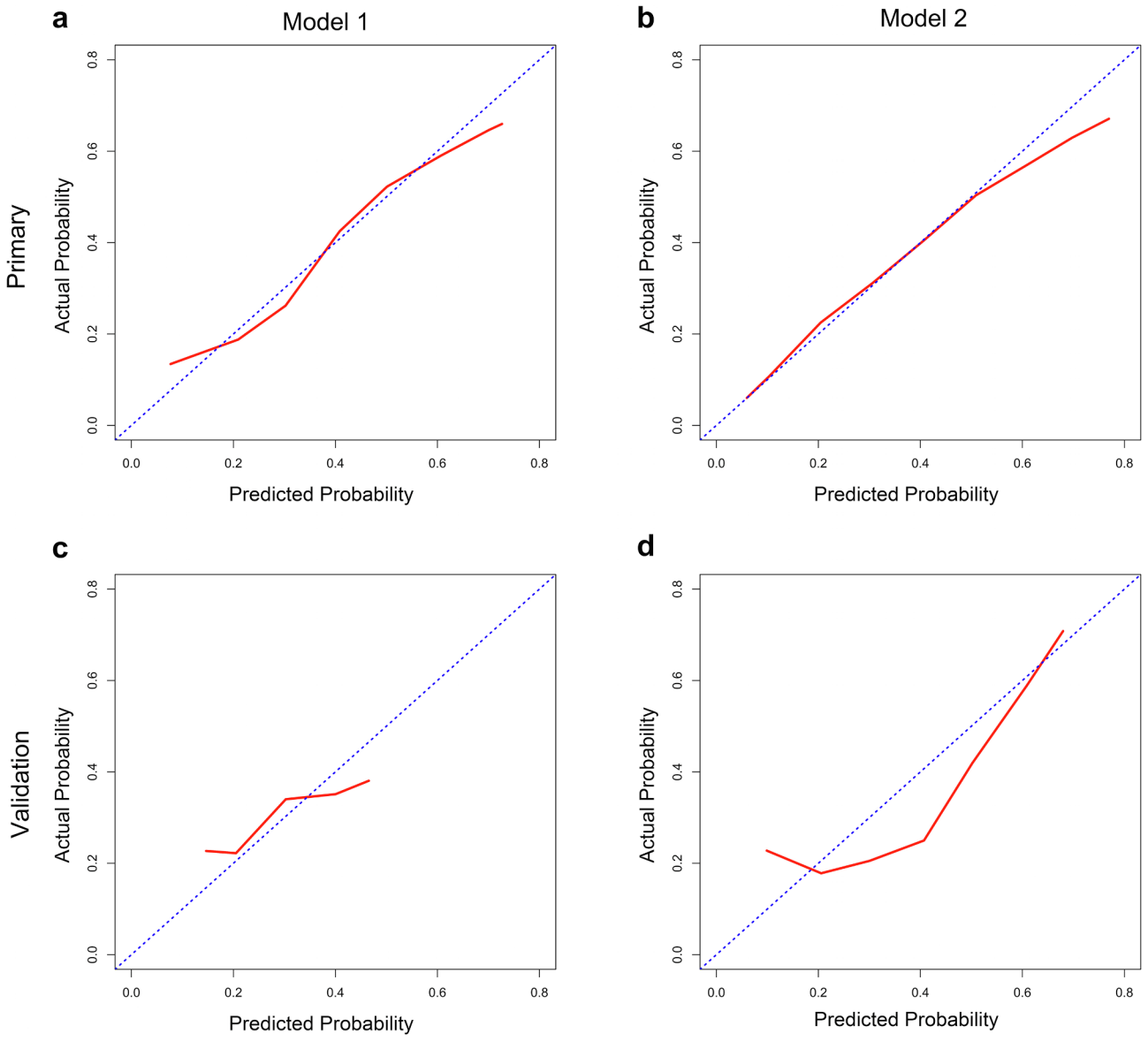

Fig. 3. Calibration curves of nomograms. Calibration curves of the Model 1 and Model 2 in the primary (a and b) and validation cohort (c and d).

was found to be associated with an increased risk of venous thromboembolism in a linear dose-response manner, which is detrimental for free flap transfer, and this association was independent of and not modified by inflammation [36]. Although the underlying mechanisms between inflammation and complications remain to be elucidated, our results indicate that the ANS can be used as an independent predictive indicator for fibula free flap reconstruction for mandibulofacial defects.

Besides, fluid infusion rate, vasopressor administration, blood transfusion, radiotherapy history and smoking status were also included in our nomogram, which is consistent with previous findings [20,37,38]. The combination of these factors in the nomogram augmented the predictive power, which further demonstrated the crucial roles of these factors in predicting the likelihood of postoperative complications.

Defining the probability of postoperative complications has been a subject of great importance because these complications not only affecting convalescence but also delay the administration of systemic adjuvant therapies in patients at high risk. There have been a plethora of studies aiming to determine the independent risk factors of outcomes after vascularized fibula flap reconstruction through means of multivariable regression analysis [37,39], but these studies failed to generate an applicable instrument that estimates individual risk by incorporating demonstrated risk factors. As an alternative, a nomogram, unlike multivariate regression analysis, is a graphical depiction of a statistical model that calculates the probability of a particular outcome for an individual patient with satisfactory accuracy [15,40]. Even though nomogram has it own limitations such as the performance of nomogram could be highly variable when the covariates measurement varied, and the effects of nomogram-assisted decisions on patient outcomes still need to be investigated [15], nomograms have been established to predict short-term and long-term outcomes in a variety of cancer types, surgeries and diseases [16–19]. Therefore, we developed and validated nomograms with and without the ANS to predict postoperative complications in our study. After comparison in accuracy and potential clinical benefit, the nomogram incorporating the ANS was found to have the ability to predict an individual likelihood of postoperative complication. In doing so, we further interpreted the clinical significance of the risk factors discovered in the present study and previous studies.

To justify the clinical usefulness of the nomograms, we assessed

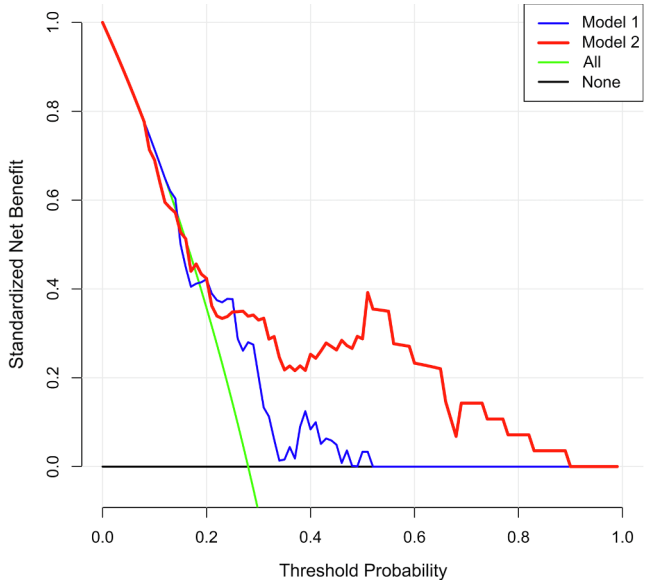

Fig. 4. Decision curves of the nomograms. The y-axis measures the standardized net benefit. The threshold probability is presented on the x-axis. The blue line represents the model without the ANS (Model 1). The red line represents the nomogram incorporating the ANS into the analysis (Model 2). The green line represents the assumption that all patients have complications. The black line represents the assumption that no postoperative complication has occurred. the threshold probability could be set between 20% and 50% when the benefit of using Model 1 was more than either the treat-all or treat-none scheme, while the threshold probability could be set between 20% and almost 90% when the benefit of using Model 2 was more than either the treat-all or treat-none scheme. For example, if the personal threshold probability of a patient is 50% (ie, the patient would opt for treatment if his probability was > 50%), then the patient will get more benefit when using the model 2 to make the decision of whether to undergo further treatment, with added benefit than the treat-all scheme or treat-none scheme. Besides. The standardized net benefit of Model 2 was higher than Model 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

whether nomogram-assisted decisions would improve patient outcomes by using DCA [23]. Although a large-scale independent prospective multicenter validation cohort is the preferred study design to assess the generalizability of the reported nomogram, the effort to fully control for bias for all relevant risk factors and outcomes and to minimize loss of follow-up in different institutions is daunting. Our nomogram incorporating the ANS showed a considerable range of thresholds, from approximately 0.2–0.9. The DCA used in this study, which enables the evaluation of clinical relevance without the requirement for additional validation data in a traditional decision-analytic approach, justified that the presented nomogram incorporating inflammatory biomarkers and clinical risk factors holds great potential for clinical application for predicting postoperative complications.

There are still several limitations. Firstly, the statistical model still has some room for improvement as the nomograms were established based on a retrospective study of medical records and thus has its own inherent limitations. In this regard, a prospective study to confirm the results would be valuable. Secondly, surgical manipulation may has influence on patients' short-term outcome, which should be taken into consideration in our study. Thirdly, intraoperative intervention to control systemic inflammation and postoperative inflammatory biomarkers should be integrated into the study considering the significant predictive value of preoperative systemic inflammation, or a more potent learning machine to predict the probability of complications should be designed, which we plan to pursue in the near future.

Conclusion

In the present study, we developed and validated a nomogram which included inflammatory biomarker, demographic data and other clinical risk factors to predict postoperative complications after vascularized fibula flap reconstruction. The proposed nomogram demonstrates the pivotal role of systemic inflammation for predicting complications. Therefore, clinicians could now apply the nomogram to evaluate the likelihood of a patient developing complications and to make personalized clinical decisions regarding management options.

Declaration of Competing Interest

None declared.

Acknowledgements

The authors acknowledge the support of Pro. Saw from Sun Yat-sen Memorial Hospital for assistance in the editing of this manuscript.

Funding

This work was supported by National Natural Science Foundation of China [grant number 81471352].

Role of the funding source

The funding source had no involvement in study design, collection, analysis and interpretation of data, writing of the report, or decision to submit the article for publication.

Ethical approval

The study protocol was approved by the Institutional Review Board (IRB) of Sun Yat-Sen Memorial Hospital.

References

[1] Okay D, Al Shetawi AH, Moubayed SP, Mourad M, Buchbinder D, Urken ML. Worldwide 10-year systematic review of treatment trends in fibula free flap for mandibular reconstruction. J Oral Maxillofac Surg 2016;74:2526–31.
[2] Bourget A, Chang JT, Wu DB, Chang CJ, Wei FC. Free flap reconstruction in the head and neck region following radiotherapy: a cohort study identifying negative outcome predictors. Plast Reconstr Surg 2011;127:1901–8.
[3] Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg 1999;103:403–11.
[4] Ryan MW, Hochman M. Length of stay after free flap reconstruction of the head and neck. Laryngoscope 2000;110:210–6.
[5] Smolka W, Iizuka T. Surgical reconstruction of maxilla and midface: clinical outcome and factors relating to postoperative complications. J Craniomaxillofac Surg 2005;33:1–7.
[6] McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 2003;90:215–9.
[7] Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer 2012;107:695–9.
[8] Chan JC, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg 2017;265:539–46.
[9] Josse JM, Cleghorn MC, Ramji KM, Jiang H, Elnahas A, Jackson TD, et al. The neutrophil-to-lymphocyte ratio predicts major perioperative complications in patients undergoing colorectal surgery. Colorectal Dis 2016;18:O236–42.
[10] Miyakita H, Sadahiro S, Saito G, Okada K, Tanaka A, Suzuki T. Risk scores as useful predictors of perioperative complications in patients with rectal cancer who received radical surgery. Int J Clin Oncol. 2017;22:324–31.
[11] Son HJ, Roh JL, Choi SH, Nam SY, Kim SY. Nutritional and hematologic markers as predictors of risk of surgical site infection in patients with head and neck cancer undergoing major oncologic surgery. Head Neck 2018;40:596–604.
[12] McCluney SJ, Giakoustidis A, Segler A, Bissel J, Valente R, Hutchins RR, et al. Neutrophil: lymphocyte ratio as a method of predicting complications following hepatic resection for colorectal liver metastasis. J Surg Oncol 2018;117:1058–65.
[13] Kao HK, Löfstrand J, Loh CY, Lao WW, Yi JS, Chang YL, et al. Nomogram based on albumin and neutrophil-to-lymphocyte ratio for predicting the prognosis of patients

with oral cavity squamous cell carcinoma. Sci Rep 2018;8:13081.
[14] Sun X, Wang J, Liu J, Chen S, Liu X. Albumin concentrations plus neutrophil lymphocyte ratios for predicting overall survival after curative resection for gastric cancer. Onco Targets Ther. 2016;9:4661–9.
[15] Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16:e173–80.
[16] Tang LQ, Li CF, Li J, Chen WH, Chen QY, Yuan LX, et al. Establishment and validation of prognostic nomograms for endemic nasopharyngeal carcinoma. J Natl Cancer Inst 2015;108:djv291.
[17] Yang Y, Zhang YJ, Zhu Y, Cao JZ, Yuan ZY, Xu LM, et al. Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study. Leukemia 2015;29:1571–7.
[18] Callegaro D, Miceli R, Bonvalot S, Ferguson P, Strauss DC, Levy A, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. Lancet Oncol 2016;17:671–80.
[19] Raman JD, Lin YK, Shariat SF, Krabbe LM, Margulis V, Arnouk A, et al. Preoperative nomogram to predict the likelihood of complications after radical nephroureterectomy. BJU Int 2017;119:268–75.
[20] Brady JS, Desai SV, Crippen MM, Eloy JA, Gubenko Y, Baredes S, et al. Association of anesthesia duration with complications after microvascular reconstruction of the head and neck. JAMA Facial Plast Surg 2018;20:188–95.
[21] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.
[22] Sauerbrei W, Boulesteix AL, Binder H. Stability investigations of multivariable regression models derived from low- and high-dimensional data. J Biopharm Stat 2011;21:1206–31.
[23] Vickers AJ, Cronin AM, Elkin EB, Gonen M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. BMC Med Inf Decis Making 2008;8:53.
[24] Ayça B, Akın F, Celik O, Sahin I, Yildiz SS, Avci II, et al. Neutrophil to lymphocyte ratio is related to stent thrombosis and high mortality in patients with acute myocardial infarction. Angiology 2015;66:545–52.
[25] Don BR, Kaysen G. Poor nutritional status and inflammation: serum albumin: relationship to inflammation and nutrition. Semin Dial 2004;17:432–7.
[26] Yin M, Si L, Qin W, Li C, Zhang J, Yang H, et al. Predictive value of serum albumin level for the prognosis of severe sepsis without exogenous human albumin administration. J Intensive Care Med 2018;33:687–94.
[27] Liu Z, Jin K, Guo M, Long J, Liu L, Liu C, et al. Prognostic value of the CRP/Alb ratio, a novel inflammation-based score in pancreatic cancer. Ann Surg Oncol 2017;24:561–8.
[28] Moyes LH, Leitch EF, McKee RF, Anderson JH, Horgan PG, McMillan DC. Preoperative systemic inflammation predicts postoperative infectious complications in patients undergoing curative resection for colorectal cancer. Br J Cancer 2009;100:1236–9.
[29] Venturi ML, Davison SP, Caprini JA. Prevention of venous thromboembolism in the plastic surgery patient: current guidelines and recommendations. Aesthet Surg J. 2009;29:421–8.
[30] Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med 2010;38:S26–34.
[31] Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood 2019;133:906–18.
[32] Kimball AS, Obi AT, Diaz JA, Henke PK. The emerging role of NETs in venous thrombosis and immunothrombosis. Front Immunol 2016;7:236.
[33] Albayati MA, Grover SP, Saha P, Lwaleed BA, Modarai B, Smith A. Postsurgical inflammation as a causative mechanism of venous thromboembolism. Semin Thromb Hemost 2015;41:615–20.
[34] Daley J, Khuri SF, Henderson W, Hur K, Gibbs JO, Barbour G, et al. Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: results of the national veterans affairs surgical risk study. J Am Coll Surg 1997;185:328–40.
[35] Morotti A, Marini S, Lena UK, Crawford K, Schwab K, Kourkoulis C, et al. Significance of admission hypoalbuminemia in acute intracerebral hemorrhage. J Neurol 2017;264:905–11.
[36] Kunutsor SK, Seidu S, Katechia DT, Laukkanen JA. Inverse association between serum albumin and future risk of venous thromboembolism: interrelationship with high sensitivity C-reactive protein. Ann Med 2018;50:240–8.
[37] Wu H, Liu F, Ji F, Guo M, Wang Y, Cao M. Identification of independent risk factors for complications: a retrospective analysis of 163 fibular free flaps for mandibulofacial reconstruction. J Oral Maxillofac Surg 2018;76:1571–7.
[38] Nelson JA, Fischer JP, Grover R, Mirzabeigi MN, Nelson P, Wes AM, et al. Intraoperative perfusion management impacts postoperative outcomes: an analysis of 682 autologous breast reconstruction patients. J Plast Reconstr Aesthet Surg 2015;68:175–83.
[39] Eskander A, Kang S, Tweel B, Sitapara J, Old M, Ozer E, et al. Predictors of complications in patients receiving head and neck free flap reconstructive procedures. Otolaryngol Head Neck Surg 2018;158:839–47.
[40] Grotenhuis BA, van Hagen P, Reitsma JB, Lagarde SM, Wijnhoven BP, van Berge Henegouwen MI, et al. Validation of a nomogram predicting complications after esophagectomy for cancer. Ann Thorac Surg 2010;90:920–5.