ORIGINAL ARTICLE
HEAD AND NECK SURGERY AND ONCOLOGY
DOI: 10.5152/B-ENT.2021.21539

Inflammatory indices predict pharyngocutaneous fistula formation after total laryngectomy

Levent Yücel[1], Sibel Yıldırım[2], Hasay Guliyev[2], Hazan Başak[2], Zahide Çiler Büyükatalay[2], Süha Beton[2]

[1]Department of Otorhinolaryngology, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Turkey
[2]Department of Otorhinolaryngology, Ankara University Faculty of Medicine, Ankara, Turkey

Cite this article as: Yücel L, Yıldırım S, Guliyev H, Başak H, Büyükatalay ZÇ, Beton S. Inflammatory indices predict pharyngocutaneous fistula formation after total laryngectomy. B-ENT 2021; 17(2): 98-103.

ABSTRACT

Objective: Inflammatory indices (IIs), such as the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and prognostic nutritional index (PNI) reflect the prognosis of several types of solid tumors, including laryngeal cancer. To the best of our knowledge, with the exception of NLR, the role of IIs in the prediction of pharyngocutaneous fistula (PCF) has not been investigated, and we aimed to do so in this study.

Methods: A total of 155 patients who underwent total laryngectomy (TL) from January 2010 to November 2020 were retrospectively reviewed.

Results: The PCF incidence was 31.6%. When the incidence of PCF was compared on the basis of IIs, its association with SII, NLR, PLR, and MLR was statistically significant (p=0.001, 0.002, 0.011, and 0.033, respectively). The cut-off values for SII, NLR, PLR, and MLR were 706, 2.90, 136, and 0.33, respectively. The correlation between PCF and the cut-off values of SII, NLR, and PLR was statistically significant (p=0.015, 0.007, and 0.033, respectively).

Conclusion: Our results suggest that pretreatment SII, NLR, and PLR predict PCF after TL. Patients with SII ≥ 706, NLR ≥ 2.90, and PLR ≥ 136 are at risk for the occurrence of PCF.

Keywords: Inflammatory indices, laryngeal neoplasms, laryngectomy, pharyngocutaneous fistula, swallowing disorders

Introduction

Head and neck cancer accounts for 5.3% of all cancers, and the larynx is the second most common region for head and neck cancer after the lip and oral cavity (1). Tobacco or tobacco products, alcohol, human papilloma virus infection, and diet are some of the risk factors for laryngeal cancer. Treatment for laryngeal cancer includes a combination of surgery, radiotherapy (RT), and chemotherapy (CT). Total laryngectomy (TL) and often postoperative (chemo)radiotherapy is a curative option for locally advanced laryngeal cancer. Moreover, TL can be performed for recurrence of laryngeal cancer or a dysfunctional larynx after RT and/or CT and partial laryngectomy (2).

Pharyngocutaneous fistula (PCF) is one of the most common complications of TL. In a recent meta-analysis, the incidence of PCF was reported to range between 6% and 58% (3). Some risk factors have been described in the literature, such as age, smoking, chronic obstructive pulmonary disease, coronary artery disease, T stage, previous RT, a preoperative albumin value ≤ 3.5 g/dL, a preoperative hemoglobin value ≤ 12.5 g/dL, tumor site, the type of pharyngeal closure method used, preoperative tracheostomy, and salvage surgery (3, 4). The significance of these parameters varies from study to study. Therefore, the search for new methods that predict PCF continues.

Inflammation is a defense mechanism of the body that is often triggered by pathogens or trauma. The close relationship between cancer and inflammation has been known since the 17th century (5). Moreover, chronic inflammation and infectious diseases account for 25% of cancer etiology (6). Immune mediators, such as cytokines and prostaglandins, play a critical role in carcinogenesis, tumor growth, invasion, and metastasis (7). Proinflammatory cytokines released from tumor cells affect peripheral blood counts (8, 9). Therefore, blood cell counts reflect the inflammatory status in patients with cancer. As noted in previous studies, inflammatory indices (IIs), such as the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and prognostic

Corresponding Author: Levent Yücel, leventyucel51@hotmail.com
Received: May 20, 2021 **Accepted:** July 17, 2021
Available online at www.b-ent.be

CC BY 4.0: Copyright@Author(s), "Content of this journal is licensed under a Creative Commons Attribution 4.0 International License."

nutritional index (PNI) predict outcomes in esophageal cancer, oral cancer, laryngeal cancer, and many other types of cancer (8, 10, 11). Furthermore, NLR has been found to predict PCF after TL (12). To the best of our knowledge, with the exception of NLR, IIs have not been investigated for their association with the prediction of PCF. Thus, in this study, we aimed to assess the correlation between PCF and IIs.

Methods

Study design

The medical records of the patients who underwent TL at a single tertiary institution from January 2010 to November 2020 were retrospectively reviewed.

Inclusion and exclusion criteria

All the patients with laryngeal cancer who underwent TL as confirmed by histopathological examination were included in the study. The exclusion criteria were lack of access to medical records, a history of malignancy other than laryngeal cancer, any diseases that influence the peripheral blood count (inflammatory, autoimmune, acute or chronic infectious diseases, hematological disorders, history of corticosteroid therapy, or chronic renal insufficiency), patients whose were not performed primary closure of the pharynx, and surgery for benign laryngeal pathologies.

Data collection

The following parameters were used for data collection: sex; age; comorbidities; previous RT; TN stage (according to American Joint Committee on Cancer 8th edition); presence of angiolymphatic or perineural invasion; histological differentiation grade; surgical margin; tumor site; tracheoesophageal fistula; PCF; blood counts; and SII, NLR, PLR, MLR, and PNI values. The occurrence of PCF was the main outcome. The PNI and SII values were calculated from preoperative blood counts (10 × serum albumin [g/dL]) + (0.005 × lymphocytes/μL), (neutrophil [μL] × platelet [μL])/lymphocyte, respectively.

Statistical analysis

The data were analyzed using The Statistical Package for Social Sciences version 27 .0 software (IBM Corp.; Armonk, NY, USA) with 95% confidence interval (CI). Descriptive statistics were presented as mean ± standard deviation (SD) for the numerical variables and as the number of cases (%) for the categorical variables. Normality hypotheses were tested with the Kolmogorov-Smirnov and the Shapiro-Wilks tests. Double-group comparisons of the normally distributed continuous variables were tested using the independent sample t test; those that did not show normal distribution were evaluated using the Mann-Whitney U test. The cut-off points were defined by a receiver operating characteristic (ROC) curve. The cut-off values were the point closest to the maximum sensitivity and the maximum specificity. The sensitivity and specificity of cut-off values were defined by the ROC curve. Univariate analysis of the data was performed using a 2 x 2 table (risk difference) and compared using either the Pearson's chi-squared test or Fisher's exact test. A result of $P < .05$ was considered to be statistically significant.

Main Points:

- Pharyngocutaneous fistula (PCF) is one of the most common complications of total laryngectomy (TL), and a few risk factors have been described in the literature.
- Blood cell counts reflect the inflammatory status of patients with cancer.
- Pretreatment inflammatory indices, such as systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) effectively predict PCF after TL.
- Patients with SII ≥ 706, NLR ≥ 2.90, and PLR ≥ 136 are at risk of the occurrence of PCF.

Ethics committee approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by Ankara University institutional ethics committee (date: January 15, 2021, no: İ11-698-20) and conducted in accordance with the related privacy statements and applicable regulatory requirements.

Informed consent

This was a retrospective study, and the data collection of the patients did not involve patient privacy and personal information; thus, the informed consent was exempted.

Results

The medical records of 176 patients who underwent TL were reviewed for this study. After applying the exclusion criteria, the medical records of 155 patients with laryngeal cancer were selected. The majority of the patients (147, 94.8%) were male and eight (5.2%) were female.

Twenty-one patients were excluded from the study; of whom, seven had a malignancy other than laryngeal cancer, two had a benign histopathological examination (chondroma), three had pharyngeal closure with flap, four had a preoperative history of antibiotic use for a systemic infection, and another four had a lack of access to medical records. One patient who had PCF as a late complication of RT after partial laryngectomy was also excluded from the study.

The demographic and clinical characteristics of the patients are summarized in Table 1. The mean age was 61.99 (min: 40, max: 83, SD: 8.63) years. Squamous cell carcinoma (SCC) was the most common type, accounting for 96.1% of all the cancers. Other histopathological diagnoses were listed as chondrosarcoma, alveolar rhabdomyosarcoma, high-grade mucoepidermoid carcinoma, spindle cell carcinoma, basaloid form SCC, and verrucous form SCC. TNM classification was not applied to non-epithelial tumors/sarcomas. The patients with sarcoma were not included in the T-stage classification, and no neck metastases were observed in these patients.

Primary closure of the pharynx was performed in all the patients by different surgical teams but under the supervision of the same senior surgeon (S.B.). The pharynx was closed using the same method (one-by-one suturing) in all of surgeries. The overall incidence of PCF in the series was 31.6%. The analysis for factors predisposing to PCF formation showed a statistically significant difference between PCF and non-PCF groups in terms of age, salvage surgery, previous RT, preoperative hemoglobin value, and concurrent neck dissection (Table 2).

Table 1: Demographic and clinical data of patients

Data	Sub-category of data	N (%)
Sex	Male	147 (94.8)
	Female	8 (5.2)
Age	< 60	58 (37.4)
	≥ 60	97 (62.6)
History of tobacco use	< 40 (p/y)	75 (48.4)
	≥ 40 (p/y)	80 (51.6)
Comorbidities*	HT	45 (29)
	DM	24 (15.5)
	CAD	32 (20.6)
	COPD	21 (13.5)
Previous RT		43 (27.7)
T stage	T2	10 (6.4)
	T3	62 (40.3)
	T4a	81 (52.3)
N Stage	N0	108 (69.6)
	N1	12 (7.7)
	N2b	6 (3.8)
	N2c	5 (3.2)
	N3b	21 (13.5)
Presence of perineural invasion		28 (18.1)
Presence of angiolymphatic invasion		32 (20.6)
Positive surgical margin		45 (29)
Tumor site	Supraglottic	15 (9.7)
	Glottic	4 (2.6)
	Subglottic	5 (3.2)
	Transglottic	36 (23.2)
	Supraglottic + glottic	81 (52.3)
	Glottic + subglottic	14 (9)
Histological differentiation grade	I	40 (25.3)
	II	77 (50.0)
	III	32 (20.9)
Salvage surgery		65 (41.9)

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, RT: Radiotherapy

When the incidence of PCF was compared to IIs, it was found to be statistically significant for SII, NLR, PLR, and MLR (p=0.001, 0.002, 0.011, and 0.033, respectively) (Figure 1). The cut-off values for SII, NLR, PLR, and MLR were 706, 2.90, 136, and 0.33, respectively. The sensitivity and specificity of the cut-off values are presented in Table 3. PNI was not statistically significant (p=0.438). The correlation between PCF and the cut-off values of the inflammatory indices is presented in Table 4, and

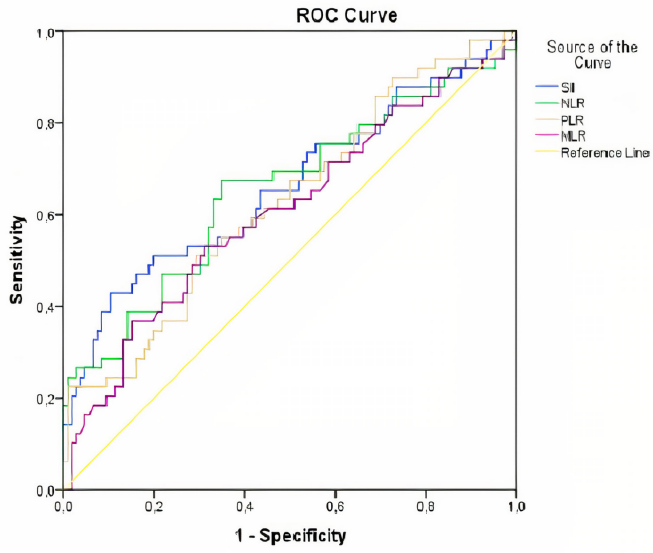

Figure 1. Receiver operating characteristic (ROC) curve related to inflammatory indices and incidence of pharyngocutaneous fistula
SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio

the values for SII, NLR, and PLR were statistically significant (p = 0.015, 0.007, and 0.043, respectively). According to the cut-off values, the absolute risk for occurrence of PCF was 18.2% for SII, 20.1% for NLR, 15.2% for PLR, and 13.8% for MLR.

The treatment method in 44 (90%) patients with PCF was conservative; however, five (10%) patients underwent surgery with a pectoralis major flap or a deltopectoral flap. Five (10%) of the patients treated with conservative methods had a recurrent permanent fistula.

Discussion

PCF is the main complication of TL that reduces the quality of life of a patient and causes a delay in administering adjuvant therapy. Therefore, the prediction and prevention of PCF has been one of the most researched topics by otolaryngologists. Age ≥ 60 years, salvage surgery, previous RT, preoperative hemoglobin < 12.5 g/dL, and concurrent neck dissection were the risk factors for PCF in our study, which is consistent with a recent meta-analysis (3). In another meta-analysis, previous RT, preoperative hemoglobin < 12.5 g/dL, location of the tumor, and T stage were the risk factors for PCF (13). Similar to our study, a low hemoglobin level and previous RT are the risk factors for PCF identified in many studies (13, 14).

Cancer and inflammation work together from the initiation of a tumor to metastasis. The role of cytokines, prostaglandins, and interleukins in cancer development and the relationship with inflammation have been clearly described (15). A greater understanding of the microenvironment of cancer, as a result of developments in technology, has resulted in the widespread use of immunotherapy in the treatment of cancer (16). The mediators released from cancer cells affect the bone marrow and the neutrophil, lymphocyte, and platelet counts reflect the immunity of the patient to inflammation and malignancies.

SII, NLR, MLR, and PLR are independent indicators calculated by the neutrophil, lymphocyte, and platelet counts; and they

Table 2: Risk factors for pharyngocutaneous fistula

Variable		PCF (n = 49) n (%)	Non-PCF (n = 109) n (%)	p	OR (95% CI)
Sex					
Male		45 (29)	102 (65.8)	0.251	0.61 (0.29–1.27)
Female		4 (2.6)	4 (2.6)		
Age					
< 60		24 (15.5)	34 (21.9)	0.043*	1.60 (1.01–2.53)
≥ 60		25 (16.1)	72 (46.5)		
Comorbidities					
HT	No	31 (20)	79 (51)	0.151	0.70 (0.44–1.12)
	Yes	18 (11.6)	27 (17.4)		
DM	No	39 (25.2)	92 (59.4)	0.249	0.71 (0.41–1.22)
	Yes	10 (6.5)	14 (9)		
CAD	No	38 (24.5)	85 (54.8)	0.706	0.89 (0.52–1.55)
	Yes	11 (7.1)	21 (13.5)		
COPD	No	41 (26.5)	93 (60)	0.492	0.80 (0.44–1.46)
	Yes	8 (5.2)	13 (8.4)		
Previous RT					
No		24 (15.5)	88 (56.8)	0.000*	5.09 (2.39–10.84)
Yes		25 (16.1)	18 (11.6)		
T stage					
T2,3		22 (14.1)	50 (33.1)	0.837	1.07 (0.54–2.13)
T4a		26 (16.7)	55 (35.9)		
N stage					
N-		36 (23.2)	72 (46.5)	0.485	0.76 (0.36–1.62)
N+		13 (8.4)	34 (21.9)		
Perineural İnvasion					
Absent		37 (23.9)	90 (58.1)	0.15.7	1.82 (0.78–4.22)
Present		12 (7.7)	16 (10.3)		
Angiolymphatic invasion					
Absent		36 (23.2)	87 (56.1)	0.218	1.65 (0.73–3.70)
Present		13 (8.4)	19 (12.3)		
Histological differentiation grade					
I-II		10 (6.7)	30 (20.1)	0.347	1.47 (0.65–3.35)
III		36 (24.2)	73 (49)		
Surgical margin					
Negative		33 (21.3)	73 (49.7)	0.500	1.28 (0.61–2.68)
Positive		16 (10..3)	29 (18.7)		
Preoperative hemoglobin					
< 12,5		20 (12.9)	20 (12.9)	0.004*	2.03 (1.30–3.16)
≥ 12,5		29 (18.7)	86 (55.5)		
Preoperative albumin					
< 3,5		12 (8.4)	29 (20.3)	0.638	1.20 (0.54–2.65)
≥ 3,5		34 (23.8)	68 (47.6)		
Concurrent neck dissection					
Absent		27 (17.4)	39 (25.2)	0.032*	1.66 (1.04–2.65)
Present		22 (14.2)	67 (43.2)		
TEF opening method					
Puncture		10 (6.5)	29 (18.7)	0.22	Not calculated
Delay		34 (21.9)	73 (47.1)		
Not opened		5 (3.2)	4 (2.6)		
Salvage surgery					
No		22 (14.2)	68 (43.9)	0.024*	2.19 (1.10–4.37)
Yes		27 (17.4)	38 (24.4)		

PCF: Pharyngocutaneous fistula; OR: Odds ratio; CI: Confidence interval; HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease; RT: Radiotherapy; TEF: Tracheoesophageal fistula; *Statistically significant

Table 3: Results of ROC analysis

Variable	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	p
SII	0.661 (0.563–0.760)	706	65.3	56.6	0.001
NLR	0.653 (0.554–0.752)	2.90	67.3	65.1	0.002
PLR	0.628 (0.532–0.723)	136	61.2	55.7	0.011
MLR	0.607 (0.507–0.706)	0.33	59.2	57.5	0.033

ROC: Receiver operating characteristic; AUC: Area under the curve; CI: Confidence interval; SII: Systemic immune-inflammation index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio

Table 4. Univariate analysis of inflammatory indices compared to pharyngocutaneous fistula

Variable	PCF (n=49) n (%)	Non-PCF (n=109) n (%)	p	OR (95% CI)
SII				
<706	17 (11)	59 (38.1)	0.015*	2,36 (1,17-4,76)
≥706	32 (20,6)	47 (30.3)		
NLR				
<2,90	15 (9,7)	57 (36,8)	0,007*	2,63 (1,28-5,40)
≥2,90	34 (21,9)	49 (316)		
PLR				
<136	16 (10,3)	53 (34,2)	0,033*	2,06 (1,01-4,18)
≥136	33 (21,3)	53 (34,2)		
MLR				
<0,33	19 (12,3)	58 (37,4)	0,065	1,90 (0,95-3,80)
≥0,33	30 (19,4)	48 (31)		

PCF: Pharyngocutaneous fistula, SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, OR: Odds ratio, CI: Confidence interval

predict survival in several types of solid tumors (17-19). In a recent study, high SII (> 891) predicted recurrence in operable laryngeal cancer in a multivariate analysis (Hazard ratio [HR] = 3.06, 95% CI: 3.42–132.64, p<0.01) (20). In a meta-analysis of 1,780 patients with laryngeal SCC, the increase in the NLR was related to disease-free survival (risk ratio=2.09, 95% CI: 1.62–2.6, p<0.001) (21). In a series of 327 patients with nasopharyngeal carcinoma, SII (HR=2.26, 95% CI: 1.40–3.66, p=0.001), NLR (HR = 1.66, 95% CI: 1.08–2.53, p=0.020), and MLR (HR =1.99, 95% CI 1.17–3.39, p=0.011) predicted overall survival (OS), and SII was superior to NLR, MLR, and PLR (22). PNI (< 45) predicts OS in patients with head and neck cancer (HR=3.74, 95% CI: 1.76–7.96, p=0.001) (23). Han et al. (24) reported that patients who had esophageal cancer and were treated with CT and RT with a PLR > 153 were at risk of esophageal fistula (HR=3.10, 95% CI: 1.615–5.952, p<0.001). PNI reflects the nutritional and immune status of patients based on the albumin value and lymphocyte count. In a retrospective study with 975 patients, multivariate analysis showed that high PNI (>56.93) was correlated with better OS (HR=0.66, 95% CI: 0.50–0.87, p=0.01) (25). In our study, no correlation between PNI and occurrence of PCF was detected.

Aires et al (12). reported that NLR > 2.5 predicted PCF after TL with an absolute risk of 23% (OR = 2.44, 95% CI: 1.18–5.03, p=0.01), which is consistent with our study findings of NLR ≥ 2.90 with an absolute risk of 20.1% (OR = 2.63, 95% CI:1.28–5.40, p=0.007). To the best of our knowledge, SII, PLR, MLR, and PNI have not yet been evaluated for their association with the incidence of PCF. In our study, SII ≥ 706, NLR ≥ 2.90, and PLR ≥ 136 predicted the incidence of PCF. According to our study, NLR ≥ 2.90 was better than the other IIs in predicting PCF.

Our study had some limitations. It was a retrospective, single-center study with a relatively small number of patients. Prospective, multi-center studies should be designed to support our preliminary results. The cut-off values of IIs should be investigated with larger populations of patients and standardized for PCF.

In conclusion, although our results need further investigation with multi-center, prospective studies; our findings suggest that pretreatment IIs, such as SII, NLR, and PLR effectively predict PCF after TL. Patients with SII ≥ 706, NLR ≥ 2.90, and PLR ≥ 136 are at risk for the occurrence of PCF.

Ethics Committee Approval: This study was approved by Ethics committee of Ankara University, (Approval No: İ11-698-20 , Date: January 15, 2021).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – L.Y., S.Y.; Design – L.Y., H.B., H.G., S.B.; Supervision – H.B., Z.Ç.T., S.B.; Resources – N.A.; Materials – N.A.; Data Collection and/or Processing – L.Y., S.Y., H.G., H.B.; Analysis and/or Interpretation – L.Y., S.B.; Literature Search – L.Y., S.Y., H.G., H.B., Z.Ç.T., S.B.; Writing Manuscript – L.Y.; Critical Review – H.B., Z.Ç.T., S.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Aupérin A. Epidemiology of head and neck cancers: an update. Curr Opin Oncol 2020; 32: 178-86. [Crossref]
2. Bril SI, Pezier TF, Tijink BM, Janssen LM, Braunius WW, de Brie R. Preoperative low skeletal muscle mass as a risk factor for pharyngocutaneous fistula and decreased overall survival in patients undergoing total laryngectomy. Head Neck 2019; 41: 1745-55. [Crossref]
3. Wang M, Xun Y, Wang K, et al. Risk factors of pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol 2020; 277: 585-99. [Crossref]
4. Michael RC, Das S, Mani S, et al. Pharyngocutaneous fistula following primary and salvage laryngectomy: aetiology and predictive factors. Indian J Otolaryngol Head Neck Surg 2020 August 17. [Crossref]
5. Munn LL. Cancer and inflammation. Interdiscip Rev Syst Biol Med 2017; 9: e1370. [Crossref]
6. Perwez Hussain S, Harris CC. Inflammation and cancer: an ancient link with novel potentials. Int J Cancer 2007; 121: 2373-80. [Crossref]
7. Sylman JL, Mitrugno A, Atallah M, et al. The predictive value of inflammation-related peripheral blood measurements in cancer staging and prognosis. Front Oncol 2018; 8: 78. [Crossref]
8. Lu Z, Yan W, Liang J, et al. Nomogram based on systemic immune-inflammation index to predict survival of tongue cancer patients who underwent cervical dissection. Front Oncol 2020; 10:341. [Crossref]
9. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget 2017; 8:75381. [Crossref]
10. Feng JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. J Surg Oncol 2014; 12: 58. [Crossref]
11. Shi L, Qin X, Wang H, et al. Elevated neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio and decreased platelet-to-lymphocyte ratio are associated with poor prognosis in multiple myeloma. Oncotarget 2017; 8: 18792. [Crossref]
12. Aires F, Dedivitis R, Kulcsar M, Ramos DM, Cernea CR. Neutrophil-to-lymphocyte ratio as a prognostic factor for pharyngocutaneous fistula after total laryngectomy. Acta Otorhinolaryngol Ital 2018; 38: 31. [Crossref]
13. Liang JW, Li ZD, Li SC, Fang FQ, Zhao YJ, Li YG. Pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis of risk factors. Auris Nasus Larynx 2015; 42: 353-9. [Crossref]
14. Casasayas M, Sansa A, García-Lorenzo J, et al. Pharyngocutaneous fistula after total laryngectomy: multivariate analysis of risk factors and a severity-based classification proposal. Eur Arch Otorhinolaryngol 2019; 276: 143-51. [Crossref]
15. Bottazzi B, Riboli E, Mantovani A. Aging, inflammation and cancer. Semin Immunol 2018; 40: 74-82. [Crossref]
16. Kruger S, Ilmer M, Kobold S, et al. Advances in cancer immunotherapy 2019-latest trends. J Exp Clin Cancer Res 2019; 38: 1-11. [Crossref]
17. Chen L, Kong X, Wang Z, Wang X, Fang Y, Wang J. Pre-treatment systemic immune-inflammation index is a useful prognostic indicator in patients with breast cancer undergoing neoadjuvant chemotherapy. J Cell Mol Med 2020; 24: 2993-3021. [Crossref]
18. Dong M, Shi Y, Yang J, et al. Prognostic and clinicopathological significance of systemic immune-inflammation index in colorectal cancer: a meta-analysis. Ther Adv Med Oncol 2020; 12: 1-14. [Crossref]
19. Takenaka Y, Oya R, Kitamiura T, et al. Platelet count and platelet-lymphocyte ratio as prognostic markers for head and neck squamous cell carcinoma: meta-analysis. Head Neck 2018; 40: 2714-23. [Crossref]
20. Demir A, Alan O, Surmeli M. Predictive values of systemic inflammation index in prognosis of patients with laryngeal cancer. Eurasian J Med Oncol 2020; 4: 49-53. [Crossref]
21. Zhao Y, Qin J, Qiu Z, Guo J, Chang W. Prognostic role of neutrophil-to-lymphocyte ratio to laryngeal squamous cell carcinoma: a meta-analysis. Braz J Otorhinolaryngol 2020 Nov 9. [Crossref]
22. Jiang W, Chen Y, Huang J, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with nasopharyngeal carcinoma: a propensity score-matched analysis. Oncotarget 2017; 8: 66075-66086. [Crossref]
23. Bruixola G, Caballero J, Papaccio F, et al. Prognostic Nutritional Index as an independent prognostic factor in locoregionally advanced squamous cell head and neck cancer. Eurasian J Med Oncol 2018; 3: e000425. [Crossref]
24. Han D, Zhang J, Zhao J, et al. Platelet-to-lymphocyte ratio is an independent predictor of chemoradiotherapy-related esophageal fistula in esophageal cancer patients. J Transl Med 2020; 8: 1163. [Crossref]
25. Fu Y, Chen SW, Chen SQ, et al. A preoperative nutritional index for predicting cancer-specific and overall survival in Chinese patients with laryngeal cancer: a retrospective study. Medicine 2016; 95: e2962. [Crossref]