Neoplasma 2022; 69(5): 1246–1252

doi:10.4149/neo_2022_220422N441

Preoperative circulating fibrinogen to albumin ratio in predicting 5-year prognosis of oral cancer radical surgery

Hong ZHU[1,#], Wei ZHANG[2,#], Pu YE[2], Meng WU[2,*]

[1]Department of Pharmacy, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huai'an, Jiangsu, China; [2]Department of Oral and Maxillofacial Surgery, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huai'an, Jiangsu, China

**Correspondence: hayywm@njmu.edu.cn*
[#]Contributed equally to this work.

Received April 22, 2022 / Accepted July 6, 2022

Accurate prediction of oral cancer (OC) prognosis before surgery is the key to treatment. The prognosis of OC is mainly based on the Tumor-Node-Metastasis (TNM) staging system, but TNM staging cannot accurately predict clinical prognosis. Current research results show that systemic inflammatory and nutritional markers can influence the postoperative prognosis and outcome of malignant tumors. The objectives of this research are to explore the preoperative blood fibrinogen and albumin in OC patients and to determine the predictive validity of the fibrinogen to albumin ratio (FAR) over 5 years of follow-up. This retrospective cohort study queried The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University database and identified 157 cases of OC operations performed between 2014 and 2016. Survival curves were presented by the Kaplan-Meier method. Univariate and multivariate analyses were used to assess clinical value for patients with radical surgery. The FAR revealed a good prediction for 5-year cancer-specific survival (CSS). The optimal cut-off value for FAR was 0.072. Multivariate logistic regression analyses revealed that FAR was an independent risk factor for survival. Increased FAR (>0.072) is negatively associated with the CSS of patients (log-rank test, $p<0.01$). The preoperative FAR may provide a significant predictor of cancer-specific survival in oral cancer patients undergoing radical surgery.

Key words: oral cancer, fibrinogen to albumin ratio, biomarkers, prognosis

Oral cancer (OC) ranks as the sixth most common carcinoma, and it is a matter of global concern [1]. The incidence of oral cancer among young people is increasing, mainly due to the prevalence of smoking, alcohol consumption, and betel nut chewing among young people [2]. Unfortunately, most patients are in an advanced stage of oral cancer and miss the best time for treatment. Despite continuous improvements in prevention and treatment, OC outcomes remain poor, and 5-year survival rates are less than 50% [3]. Most predictions of survival are based on postoperative diagnosis, including pathology, but there is no recognized prognostic factor before radical surgery for oral cancer. In fact, in the same tumor staging of oral cancer, the choice of tumor surgery is still controversial [4]. For example, whether lymph node dissection should be performed for stage I and II oral cancer is still not recognized [5, 6]. This requires us to find a new marker to predict the prognosis of patients before oral cancer surgery.

Inflammatory factors play a substantial role in the initial and developmental stages of cancer [7]. Tumor cells can recruit inflammatory factors to promote adhesion and form a "protective coat" to achieve immune evasion [8, 9]. Recent studies had confirmed that several inflammation-based biomarkers, such as fibrinogen and neutrophil-to-lymphocyte ratio, can predict poor outcomes in head and neck malignant tumors [10–12].

Nutritional status is one of the important indicators of cancer incidence and mortality [13]. International Agency for Research on Cancer (IARC) had validated that low nutrient levels promote cancer development [1]. Albumin, which makes up more than half of blood protein and is generated and released by the liver, represents the protein status of the blood and internal organs [14]. Recent work has established that balanced nutrition improves outcomes for patients with head and neck cancer [15]. Moreover, the combination of fibrinogen and albumin improves the accuracy of predicting long-term survival in patients with gastric cancer [16]. To date, the combined effect of fibrinogen and albumin in oral cancer has still not been systematically investigated.

Therefore, this study set out based on the levels of fibrinogen and albumin to more accurately predict the prognosis

of oral cancer patients. The aim of this investigation has been to explore the significance of FAR in the long-term survival of oral cancer patients.

Patients and methods

Patient population. A retrospective analysis was done on oral cancer patients treated with radical oral cancer surgery in the Department of Oral and Maxillofacial Surgery, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. Patients undergoing radical surgery for OC between February 2014 and November 2016 were included. The exclusion criteria were as follows: 1) the tumor was not pathologically diagnosed as oral cavity cancer; 2) patients with distant metastases before surgery; 3) patients who received radiotherapy and chemotherapy before surgery. Together, 157 patients were enrolled for further analysis [17]. A flowchart summarizing the present study is shown in Figure 1. All patients were followed for up to 5 years if the patients were still alive.

Data collection and definitions. We used the electronic information system of our medical institution to query the relevant information of the patients during hospitalization. Since some patients have died, our study was approved by our institutional ethics committee without the need for informed consent, this study does not require a questionnaire. Basic information on patients, body mass index (BMI), medical history, preoperative laboratory data, and annual follow-up data were derived from the medical record database of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. Albumin concentrations were detected by a blood analyzer (Switzerland). A blood analyzer (Japan) detects the concentration of plasma fibrinogen. The formula for calculating FAR is as follows: FAR = plasma fibrinogen (g/l) / serum albumin (g/l). OC was diagnosed according to histopathological evaluation, and the histological grade was staged according to the AJCC-TNM staging [18]. Cancer-specific survival refers to the time from the first diagnosis to death due to oral cancer [19].

Statistical analysis. The evaluation value of the index is evaluated by the area under the receiver operating characteristic (ROC) curve based on the maximum Youden index. Univariable and multivariable analyses were used to evaluate the prognostic significance of included factors. A Chi-square or Fisher's exact test was performed on categorical data. Continuous variables were analyzed using the Mann-Whitney U test. Cancer-specific survival was assessed using multivariate analysis and Kaplan-Meier analysis. The data analysis was performed using IBM SPSS, version 22 (IBM). Statistical tests were two-sided and considered significant with a p-value <0.05.

Results

Clinicopathological characteristics of the patients with OC. The clinicopathological characteristics are shown in Table 1. T stage (p=0.0119) and pathological grade (p=0.0009) were associated with 5-year CSS (Table 1).

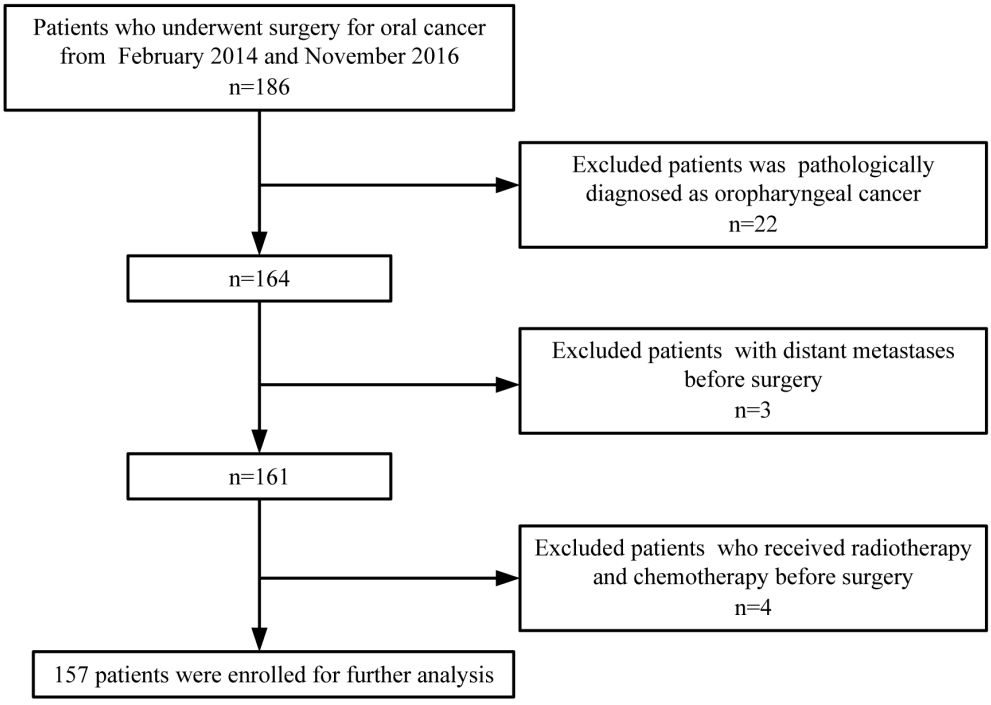

Figure 1. Flow diagram of the cases analyzed.

ROC Analysis. Using ROC curve analysis, we identified the survival prediction values for fibrinogen, albumin, and FAR. Figure 2 shows the ROC curves and AUC results: the curve of fibrinogen (AUC=0.828, Figure 2A); the curve of albumin (AUC=0.860, Figure 2B); the curve of FAR (AUC=0.927, Figure 2C). The preoperative FAR showed a relatively better predictive role in oral cancer prognosis than fibrinogen and albumin alone (Figure 2). Using X-tile software, the optimal cut-off value for preoperative fibrinogen, albumin, and FAR was determined as 3.9 g/l, 39.3 g/l, and 0.072, respectively (Figure 3).

Association of preoperative FAR with clinicopathologic variables. Patients were divided into two groups based on the optimal cut-off value (FAR >0.072 vs. FAR <0.072). In Table 2, the clinicopathological characteristics of patients in the FAR high group and FAR low group are listed. FAR was associated with tumor size (p=0.0021) and pathological grade (p=0.0020) (Table 2).

Prognostic significance of preoperative FAR in oral cancer. In total, 12 clinicopathological parameters were included in univariate and multivariate analysis (Table 3). Multivariate analysis showed FAR was an independent prognostic factor for CSS (HR for FAR: 8.091; 95% CI: 1.847–35.443; p=0.006). Patients with a high FAR portend a poor prognosis (Figure 3).

Furthermore, the stratified analysis indicated that a high FAR was unfavorable to the prognosis of OC patients with T1–T2 (p<0.0001, Figure 4A), pathological grade I (p=0.0002, Figure 4C,) and pathological grade II–III (p=0.0361, Figure 4D) but not with T3–T4 (p=0.1871, Figure 4B).

Discussion

The relationship between OC and chronic inflammation has been widely investigated in recent years. Previous studies have established that inflammatory factors play an essential role in the initiation and propagation of OC [2, 20]. Moreover, emerging evidence indicates that inflammatory factors can affect the tumor microenvironment and promote tumor cell invasion and metastasis [21]. Additionally, a study has demonstrated that the prognostic value of inflammation-related markers in head and neck cancer and chronic periodontitis has systemic effects, and that it has a high risk of developing different types of cancer, especially oral cancer [22]. Considering all of this evidence, it seems that understanding the pathogenesis of inflammatory factors can better

Table 1. Comparison of clinical characteristics of the enrolled subjects (n=157).

Variables	CSS <5 year (n=60)	CSS ≥5 year (n=97)	p-value χ^2
Age			0.0891
<60	15	37	
≥60	45	60	
Gender			0.1330
Male	26	54	
Female	34	43	
Hypertension			0.3356
No	45	79	
Yes	15	18	
Smoking			0.6505
No	54	85	
Yes	6	12	
Alcohol			0.3195
No	58	89	
Yes	2	8	
BMI (kg/m^2)			0.4612
<25	40	59	
≥25	20	38	
T stage			**0.0119**
T1–T2	53	69	
T3–T4	7	28	
Cervical node metastasis			0.8504
N0	46	76	
N+	14	21	
Pathological grade			**0.0009**
I	35	80	
II–III	25	17	

Abbreviations: BMI-body mass index; CSS-cancer-specific survival

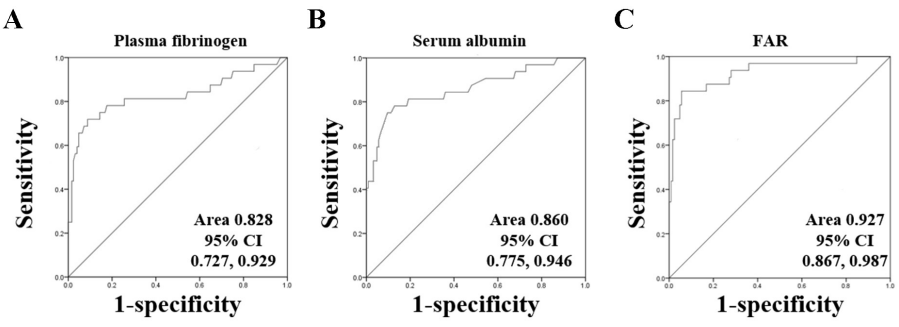

Figure 2. ROC curve for the fibrinogen (A), albumin (B), and FAR (C) in OC patients. Fibrinogen, albumin, FAR, and CSS were used as the test and state variables, respectively. The area under the curve is 0.828 (fibrinogen), 0.860 (albumin), and 0.931 (FAR), respectively. Abbreviations: ROC-receiver operating characteristic; CI-confidence interval; FAR-fibrinogen-to-albumin ratio; OC-oral cancer; CSS-cancer-specific survival

Table 2. Comparison of clinical characteristics of the enrolled subjects (n=157).

Variables	FAR high (n=100)	FAR low (n=57)	p-value χ^2
Age			0.1462
<60	29	23	
≥60	71	34	
Gender			0.7511
Male	50	30	
Female	50	27	
Hypertension			0.6895
No	78	46	
Yes	22	11	
Smoking			0.1991
No	91	48	
Yes	9	9	
Alcohol			0.3520
No	95	52	
Yes	5	5	
BMI (kg/m^2)			0.1630
<25	59	40	
≥25	41	17	
T stage			**0.0021**
T1–T2	70	52	
T3–T4	30	5	
Cervical node metastasis			0.0605
N0	73	49	
N+	27	8	
Pathological grade			0.0020
I	65	50	
II–III	35	7	

Abbreviations: BMI-body mass index; FAR-fibrinogen-to-albumin ratio

understand the occurrence, development, and prognosis of oral cancer and provide reliable prognostic factors for clinical practice.

Fibrinogen affects the interaction between tumor cells and blood components, and it can promote the adhesion of platelets and growth factors to further create a favorable environment for tumor invasion and metastasis [23]. In an investigation of fibrinogen, Perisanidis et al. showed that elevated plasma fibrinogen levels before treatment had a positive association with shorter survival in patients with solid tumors [10]. Similarly, Selzer reported that fibrinogen levels before treatment may be one of the markers of prognosis in head and neck cancer [24]. Alternatively, nutrition plays an essential role in the prognosis of cancer patients. One longitudinal study found that 80% of head and neck cancer patients' cancer is related to their lifestyle and malnutrition [15]. Due to the convenience of collection of serum albumin, it has been adopted clinically as a marker of nutritional level in clinical practice, and hypoalbuminemia is also a marker of malnutrition. This view is supported by Loftus who shows that serum albumin is one of the most common risk factors for malignancy and the strongest predictor of recovery after surgery [14]. Albumin accumulates at sites of inflammation and tumors and is an ideal drug delivery platform, widely used in anti-inflammatory and cancer therapy [25, 26].

The combined significance of multiple indicators plays a significant role in the prognosis of cancer. Fibrinogen and albumin are important indicators of inflammation in oral cancer. Previous studies have established that FAR is a key prognostic factor before resectioning of malignant tumors such as colorectal cancer, ovarian cancer, non-small cell lung cancer, and gallbladder cancer, and patients with higher FAR

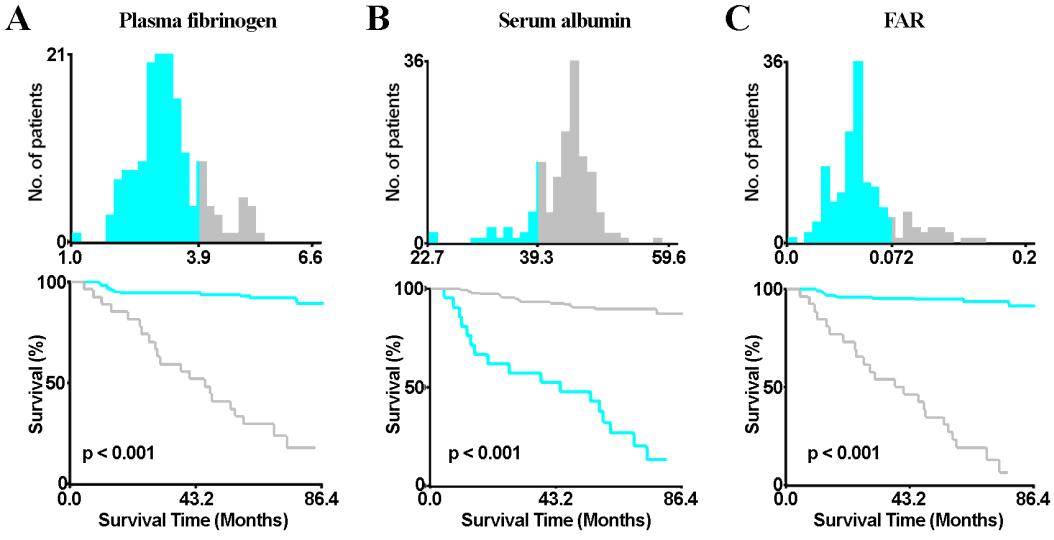

Figure 3. Kaplan-Meier curves for CSS according to the fibrinogen (A), albumin (B), and FAR (C) in OC patients. The Kaplan-Meier survival analysis was performed when the optimal cut-off values of fibrinogen, albumin, and FAR at diagnosis were 3.9 g/l (A), 39.3 g/l (B), and 0.072 (C), respectively. Different fibrinogen (A), albumin (B), and FAR (C) have significant differences in the long-term survival rate of oral cancer patients, with p-values <0.01. Abbreviations: FAR-fibrinogen-to-albumin ratio; OC-oral cancer; CSS-cancer-specific survival

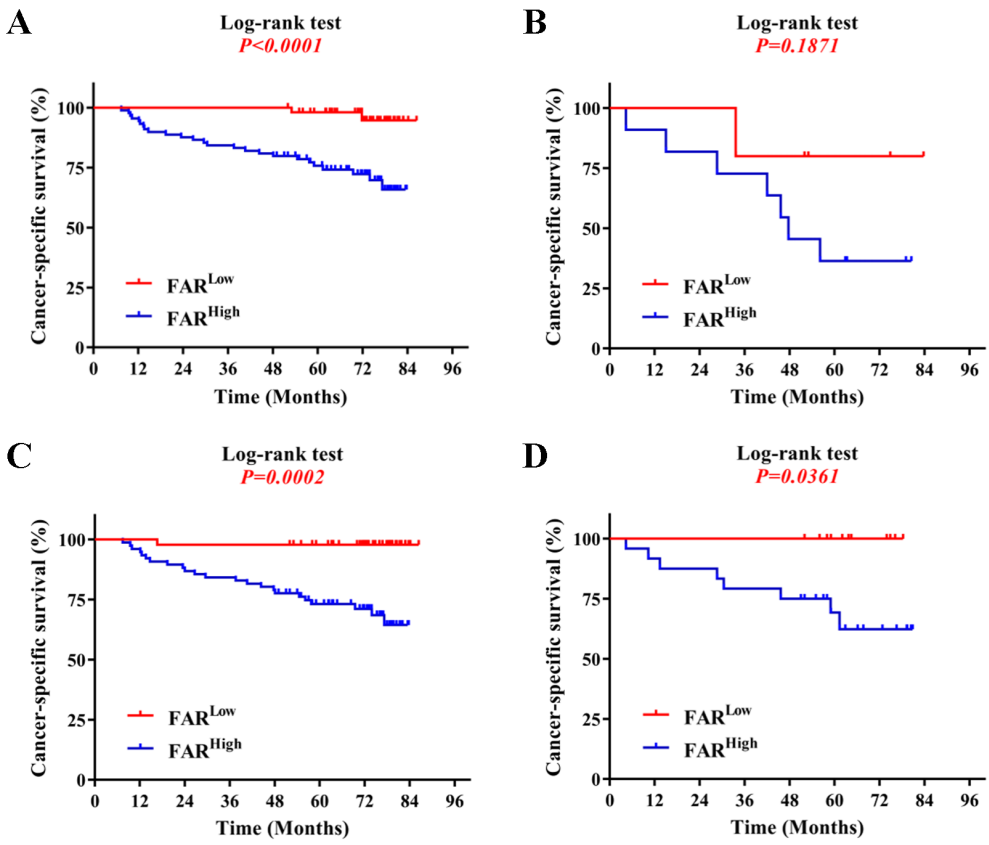

Figure 4. CSS based on the FAR in OC patients with T1–T2 (A), patients with T3–T4 (B), patients with pathological grade I (C), and patients with pathological grade II–III (D). When the cut-off of FAR at diagnosis was 0.072 was applied to the subgroup Kaplan-Meier survival analysis, there were significant differences between high FAR and low FAR groups in T1–T2 (A), pathological grade I (C), pathological grade II–III (D), but not in T3–T4 (B). Abbreviations: FAR-fibrinogen-to-albumin ratio; OC-oral cancer; CSS-cancer-specific survival

Table 3. Univariate and multivariate analyses of prognostic factors in 157 patients with oral cancer.

Variable	Univariate survival analysis			Multivariate survival analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age	1.847	0.903–3.779	0.093			
Gender	1.608	0.722–3.581	0.245			
Hypertension	1.187	0.879–3.924	0.105			
Smoking	0.785	0.239–2.577	0.690			
Alcohol	0.869	0.207–3.638	0.847			
BMI (kg/m^2)	1.057	0.516–2.163	0.880			
T stage	2.900	1.252–6.716	**0.013**	2.807	1.196–6.586	**0.018**
Cervical node metastasis	1.882	0.907–3.906	0.090	1.474	0.696–3.122	0.311
Pathological grade	2.248	1.108–4.559	**0.025**	1.954	0.950–4.017	0.069
Fibrinogen level	8.297	1.132–60.811	**0.037**	4.425	0.588–33.301	0.149
Albumin level	0.088	0.044–0.177	**<0.001**	0.181	0.088–0.372	**<0.001**
FAR	15.372	3.671–64.369	**<0.001**	8.091	1.847–35.443	**0.006**

Abbreviations: BMI-body mass index; CI-confidence interval; FAR-fibrinogen-to-albumin ratio; OC-oral cancer

levels are more likely to have higher recurrence rates and higher mortality after surgery [27–30]. Our results showed that preoperative FAR was a better prognostic marker for OC compared with fibrinogen and albumin, and these findings are consistent with those of previous studies [31, 32]. Multivariate logistic regression analyses revealed that FAR was an independent risk factor for survival. This further corroborates that FAR is a reliable postoperative predictor for oral cancer.

In the correlation analysis, we found that FAR may have a similar effect to the internationally recognized TNM stage for oral cancer. In addition, FAR was closely related to tumor size, possibly because continuous oral tumor growth is often accompanied by pain and poor feeding, and this condition can lead to systemic inflammation and malnutrition. Moreover, subgroup analysis showed that high FAR levels were associated with poorer prognosis in different tumor stages and pathological grades. However, for patients with T3–T4 tumors, there was no significant difference in survival between the high and low FAR groups, which may be due to the relatively short survival time of patients with advanced tumors or the different patient populations, which failed to reflect the difference. Based on our results, it can be expected that preoperative FAR will be of general value in assessing the postoperative prognosis of oral cancer.

The advantage of this study is that it is the first time to verify the significance of FAR in the postoperative prognosis of oral cancer, and the effect of FAR on prognosis is meaningful. However, this study has shortcomings. First, this study is based on a single-center retrospective study, and the next multi-center prospective study needs to be verified. Second, the sample size of this study is relatively small, and more samples are needed for corroboration. Third, due to the complexity of the patient's condition, the underlying disease affecting the treatment of the same disease may affect our results. Therefore, a more comprehensive study needs to be carried out. Despite these limitations, this study confirms the important clinical significance of the preoperative FAR score in oral cancer surgery.

In conclusion, this study suggests that preoperative FAR, which is convenient, affordable, and painless for patients, could be used as prospective noninvasive prognostic biomarkers for OC. A high FAR may be associated with shortened survival time in patients with OC.

Acknowledgments: This work was supported by grants from the Science and Technology Development Fund of Nanjing Medical University (Grant No. NMUB2020140).

References

[1] KUMAR M, NANAVATI R, MODI TG, DOBARIYA C. Oral cancer: Etiology and risk factors: A review. J Cancer Res Ther 2016; 12: 458–463. https://doi.org/10.4103/0973-1482.186696

[2] CHATTOPADHYAY I, VERMA M, PANDA M. Role of Oral Microbiome Signatures in Diagnosis and Prognosis of Oral Cancer. Technol Cancer Res Treat 2019; 18: 1533033819867354. https://doi.org/10.1177/1533033819867354

[3] SKLENICKA S, GARDINER S, DIERKS EJ, POTTER BE, BELL RB. Survival analysis and risk factors for recurrence in oral squamous cell carcinoma: does surgical salvage affect outcome? J Oral Maxillofac Surg 2010; 68: 1270–1275. https://doi.org/10.1016/j.joms.2009.11.016

[4] OMURA K. Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. Int J Clin Oncol 2014; 19: 423–430. https://doi.org/10.1007/s10147-014-0689-z

[5] GARREL R, POISSONNET G, MOYÀ PLANA A, FAKHRY N, DOLIVET G et al. Equivalence Randomized Trial to Compare Treatment on the Basis of Sentinel Node Biopsy Versus Neck Node Dissection in Operable T1-T2N0 Oral and Oropharyngeal Cancer. J Clin Oncol 2020; 38: 4010–4018. https://doi.org/10.1200/jco.20.01661

[6] VAN HINTE G, SANCAK T, WEIJS WLJ, MERKX MAW, LEIJENDEKKERS RA et al. Effect of elective neck dissection versus sentinel lymph node biopsy on shoulder morbidity and health-related quality of life in patients with oral cavity cancer: A longitudinal comparative cohort study. Oral Oncol 2021; 122: 105510. https://doi.org/10.1016/j.oraloncology.2021.105510

[7] OCANA A, NIETO-JIMÉNEZ C, PANDIELLA A, TEMPLETON AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. Mol Cancer 2017; 16: 137. https://doi.org/10.1186/s12943-017-0707-7

[8] BEKES EM, SCHWEIGHOFER B, KUPRIYANOVA TA, ZAJAC E, ARDI VC et al. Tumor-recruited neutrophils and neutrophil TIMP-free MMP-9 regulate coordinately the levels of tumor angiogenesis and efficiency of malignant cell intravasation. Am J Pathol 2011; 179: 1455–1470. https://doi.org/10.1016/j.ajpath.2011.05.031

[9] MCDONALD B, SPICER J, GIANNAIS B, FALLAVOLLITA L, BRODT P et al. Systemic inflammation increases cancer cell adhesion to hepatic sinusoids by neutrophil mediated mechanisms. Int J Cancer 2009; 125: 1298–1305. https://doi.org/10.1002/ijc.24409

[10] PERISANIDIS C, PSYRRI A, COHEN EE, ENGELMANN J, HEINZE G et al. Prognostic role of pretreatment plasma fibrinogen in patients with solid tumors: A systematic review and meta-analysis. Cancer Treat Rev 2015; 41: 960–970. https://doi.org/10.1016/j.ctrv.2015.10.002

[11] LUAN CW, YANG HY, TSAI YT, HSIEH MC, CHOU HH et al. Prognostic Value of C-Reactive Protein-to-Albumin Ratio in Head and Neck Cancer: A Meta-Analysis. Diagnostics (Basel) 2021; 11. https://doi.org/10.3390/diagnostics11030403

[12] MARIANI P, RUSSO D, MAISTO M, TROIANO G, CAPONIO VCA et al. Pre-treatment neutrophil-to-lymphocyte ratio is an independent prognostic factor in head and neck squamous cell carcinoma: Meta-analysis and trial sequential analysis. J Oral Pathol Med 2022; 51: 39–51. https://doi.org/10.1111/jop.13264

[13] SANZ EA, SILES MG, FERNÁNDEZ LR, ROLDÁN RV, DOMÍNGUEZ AR et al. Nutritional risk and malnutrition rates at diagnosis of cancer in patients treated in outpatient settings: Early intervention protocol. Nutrition 2019; 57: 148–153. https://doi.org/10.1016/j.nut.2018.05.021

[14] LOFTUS TJ, BROWN MP, SLISH JH, ROSENTHAL MD. Serum Levels of Prealbumin and Albumin for Preoperative Risk Stratification. Nutr Clin Pract 2019; 34: 340–348. https://doi.org/10.1002/ncp.10271

[15] MÜLLER-RICHTER U, BETZ C, HARTMANN S, BRANDS RC. Nutrition management for head and neck cancer patients improves clinical outcome and survival. Nutr Res 2017; 48: 1–8. https://doi.org/10.1016/j.nutres.2017.08.007

[16] WU ZJ, XU H, WANG R, BU LJ, NING J et al. Cumulative Score Based on Preoperative Fibrinogen and Pre-albumin Could Predict Long-term Survival for Patients with Resectable Gastric Cancer. J Cancer 2019; 10: 6244–6251. https://doi.org/10.7150/jca.35157

[17] TANG S, LIN L, CHENG J, ZHAO J, XUAN Q et al. The prognostic value of preoperative fibrinogen-to-prealbumin ratio and a novel FFC score in patients with resectable gastric cancer. BMC Cancer 2020; 20: 382. https://doi.org/10.1186/s12885-020-06866-6

[18] HUANG SH, O'SULLIVAN B. Overview of the 8th Edition TNM Classification for Head and Neck Cancer. Current treatment options in oncology 2017; 18: 40. https://doi.org/10.1007/s11864-017-0484-y

[19] BERGHEN C, JONIAU S, RANS K, DEVOS G, POELS K et al. Metastasis-directed therapy in castration-refractory prostate cancer (MEDCARE): a non-randomized phase 2 trial. BMC Cancer 2020; 20: 457. https://doi.org/10.1186/s12885-020-06853-x

[20] ABATI S, BRAMATI C, BONDI S, LISSONI A, TRIMARCHI M. Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. Int J Environ Res Public Health 2020; 17. https://doi.org/10.3390/ijerph17249160

[21] JOHNSTON FM, BECKMAN M. Updates on Management of Gastric Cancer. Curr Oncol Rep 2019; 21: 67. https://doi.org/10.1007/s11912-019-0820-4

[22] KAVARTHAPU A, GURUMOORTHY K. Linking chronic periodontitis and oral cancer: A review. Oral Oncol 2021; 121: 105375. https://doi.org/10.1016/j.oraloncology.2021.105375

[23] REPETTO O, DE RE V. Coagulation and fibrinolysis in gastric cancer. Ann N Y Acad Sci 2017; 1404: 27–48. https://doi.org/10.1111/nyas.13454

[24] SELZER E, GRAH A, HEIDUSCHKA G, KORNEK G, THURNHER D. Pre-therapeutic fibrinogen levels are of prognostic significance in locally advanced head and neck cancer. Wien Klin Wochenschr 2016; 128: 320–328. https://doi.org/10.1007/s00508-016-0963-3

[25] SLEEP D. Albumin and its application in drug delivery. Expert Opin Drug Deliv 2015; 12: 793–812. https://doi.org/10.1517/17425247.2015.993313

[26] BERN M, SAND KM, NILSEN J, SANDLIE I, ANDERSEN JT. The role of albumin receptors in regulation of albumin homeostasis: Implications for drug delivery. J Control Release 2015; 211: 144–162. https://doi.org/10.1016/j.jconrel.2015.06.006

[27] YU W, YE Z, FANG X, JIANG X, JIANG Y. Preoperative albumin-to-fibrinogen ratio predicts chemotherapy resistance and prognosis in patients with advanced epithelial ovarian cancer. J Ovarian Res 2019; 12: 88. https://doi.org/10.1186/s13048-019-0563-8

[28] DU JH, LU J. Circulating CEA-dNLR score predicts clinical outcome of metastatic gallbladder cancer patient. J Clin Lab Anal 2019; 33: e22684. https://doi.org/10.1002/jcla.22684

[29] LI SQ, JIANG YH, LIN J, ZHANG J, SUN F et al. Albumin-to-fibrinogen ratio as a promising biomarker to predict clinical outcome of non-small cell lung cancer individuals. Cancer Med 2018; 7: 1221–1231. https://doi.org/10.1002/cam4.1428

[30] SUN DW, AN L, LV GY. Albumin-fibrinogen ratio and fibrinogen-prealbumin ratio as promising prognostic markers for cancers: an updated meta-analysis. World J Surg Oncol 2020; 18:9. https://doi.org/10.1186/s12957-020-1786-2

[31] SUN F, PENG HX, GAO QF, LI SQ, ZHANG J et al. Preoperative circulating FPR and CCF score are promising biomarkers for predicting clinical outcome of stage II–III colorectal cancer patients. Cancer Manag Res 2018; 10: 2151–2161. https://doi.org/10.2147/cmar.s167398

[32] CHEN QG, ZHANG L, SUN F, LI SQ, YOU XH et al. Elevated FPR confers to radiochemoresistance and predicts clinical efficacy and outcome of metastatic colorectal cancer patients. Aging (Albany NY) 2019; 11: 1716–1732. https://doi.org/10.18632/aging.101864