Are Comorbidities Associated With Overall Survival in Patients With Oral Squamous Cell Carcinoma?

Úrsula M. Jariod-Ferrer, MD, PhD, Jose M. Arbones-Mainar, PhD,† Marina A. Gavin-Clavero, MD, PhD,‡ M. Victoria Simón-Sanz, MD, PhD,§ Ignacio Moral-Saez, MD, PhD,‖ Ana I. Cisneros-Gimeno, MD, PhD,¶ and Javier Martinez-Trufero, MD, PhD#*

Purpose: Oral squamous cell carcinoma (OSCC) is a highly prevalent type of immunogenic cancer with a low survival rate in patients with comorbidities owing to toxic habits.

Materials and Methods: A retrospective cohort study was conducted of patients with resectable OSCC at a tertiary Spanish hospital from 2011 to 2014. The primary predictor variables were comorbidity and immune biomarkers. Comorbidity was assessed using the Adult Comorbidity Evaluation–27 (ACE-27) and scored from 1 to 3 (mild to severe decompensation, respectively). The immune biomarkers were neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). The primary outcome variable was 5-year overall survival (OS). Other study variables were stage, margin, and neck management. Receiver operating characteristic curves were built for each ratio. For the survey of immune biomarkers, area under the curve was computed to determine cutoff points and investigate their association with OS. Kaplan-Meier estimates of survival and Cox proportional hazards models were used for longitudinal analysis.

Results: Overall 215 patients were identified (median age, 67 yr; range, 32 to 96 yr; median follow-up, 31 months; range, 7 to 78 months); 159 patients had at least 1 comorbid condition. Results showed that a severe comorbidity (according to the ACE-27) increased the risk of death by 4 times in patients with OSCC regardless of stage. NLR, dNLR, LMR, and PLR were associated with OS in the univariate study. Cutoff points to predict increased mortality were 3, 1.9, 2.6, and 66 for NLR, dNLR, LMR, and PLR, respectively. Age, comorbidity, stage, margins, and management of the neck were important independent predictors of decreased OS in OSCC. PLR was marginally associated with OS in the multivariate model.

Conclusion: These results suggest that comorbidity and NLR, dNLR, LMR, and PLR are associated with 5-year OS in patients with resectable OSCC.

J Oral Maxillofac Surg ■*:1-9, 2019*

*Attending Surgeon, Department of Oral and Maxillofacial Surgery, Miguel Servet University Hospital, Fellow of European Board of Oro-Maxillo-Facial Surgery, Zaragoza, Spain.

†Senior Researcher, Instituto Aragonés de Ciencias de la Salud (IACS), Instituto de Investigación Sanitaria (IIS) Aragón, Zaragoza; CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto Salud Carlos III, Madrid, Spain.

‡Attending Surgeon, Department of Oral and Maxillofacial Surgery, Miguel Servet University Hospital, Zaragoza, Spain.

§Attending Surgeon, Department of Oral and Maxillofacial Surgery, Miguel Servet University Hospital, Zaragoza, Spain.

‖Department Head, Department of Oral and Maxillofacial Surgery, Miguel Servet University Hospital, Zaragoza, Spain.

¶Professor, School of Medicine, University of Zaragoza, Zaragoza, Spain.

#Attending Physician, Department of Clinical Oncology, Miguel Servet University Hospital, Zaragoza, Spain.

Conflict of Interest Disclosures: None of the authors have any relevant financial relationship(s) with a commercial interest.

Address correspondence and reprint requests to Dr Jariod-Ferrer: Department of Oral and Maxillofacial Surgery, Miguel Servet University Hospital, Isabel la Católica 1-3, 50009 Zaragoza, Spain; e-mail: ursulajariodferrer@gmail.com

Received May 25 2018

Accepted March 8 2019

0278-2391/19/30277-0

https://doi.org/10.1016/j.joms.2019.03.007

Oral squamous cell carcinoma (OSCC) is the eighth most common cancer worldwide; despite improved diagnosis and treatment, 5-year survival remains low, with an average 5-year survival rate of 50% for all OSCC locations.[1,2] The most common location, with the worst prognosis, seems to be the tongue, although this is not confirmed in all studies.[3,4] These poor outcomes are explained by the fact that these tumors are prone to local invasion and lymph node metastases. In consequence, patients often develop locoregional recurrence and second primary tumors.[5,6]

Classically, disease stage is the single most powerful prognostic variable. Other factors, such as primary tumor size, lymph node involvement, distant metastasis, surgical margin, and perineural invasion, also influence tumor outcomes.[7] However, these parameters are not accurate enough for identifying patients at the highest risk because other factors related to the patient, such as comorbidity, also are involved. Hence, new tools are needed for the stratification of patients with OSCC. The association between comorbidity and worse prognosis has been reported and several instruments have been developed to measure comorbidity.[8] The Adult Comorbidity Evaluation–27 (ACE-27) is one of the most used instruments to measure the severity of comorbidities in patients with cancer.[9] This tool has been extensively validated in OSCC for predicting survival,[9] complications,[10] functional outcome,[11] and quality of life.[12] Comorbidities negatively influence the development of OSCC.[9]

However, in the past few years, a great amount of scientific evidence has been reported about the relation between carcinogenesis and inflammation.[13] Tumor cells promote a systemic inflammatory response, which can cause changes in the counts and ratios of different white blood cell (WBC) series. These changes have been widely studied in several types of cancer, and they are mainly mediated by the liberation of stress-related substances[14] and proinflammatory cytokines, such as tumor necrosis factor-α. This immune response can affect the outcome of tumor cells and therefore can be considered a potential biomarker of tumor progression and prognosis. In this context, several ratios derived from peripheral blood, such as the neutrophil-to-lymphocyte ratio (NLR),[15] derived NLR (dNLR),[16] platelet-to-lymphocyte ratio (PLR),[17] and lymphocyte-to-monocyte ratio (LMR),[18] have been investigated as useful prognostic indicators in different cancer subtypes, including OSCC.

The specific aims of the present study were to estimate comorbidity, calculate immune biomarkers, and investigate their association with patients' overall survival (OS).

Materials and Methods

To address the research purpose, the authors designed and implemented a retrospective cohort study. The study population was composed of all patients presenting for evaluation and management of resectable OSCC from January 2011 through December 2014 at the Miguel Servet University Hospital (Zaragoza, Spain).

To be included in the study sample, patients *1)* had to be treatment naive with a histopathologic diagnosis of OSCC; *2)* have no history of other cancer in the head and neck region; *3)* have available blood samples with absolute neutrophil, lymphocyte, monocyte, and platelets counts; *4)* have no hematologic disease or infection at the time of diagnosis; and *5)* have clinical stages I to IV and be candidates for surgery. Patients were excluded as study subjects if they had an OSCC treated with chemotherapy and radiotherapy.

The primary predictor variables investigated were comorbidity and immune biomarkers. Comorbidities were assessed using the ACE-27[19] and scored from 1 to 3 according to severity (mild, moderate, and severe, respectively). The ACE-27 includes 27 different comorbid ailments from different organ systems. Overall comorbidity score is assigned according to the highest single scoring ailment, except when at least 2 grade 2 ailments are present; in this situation, the score is designated grade 3. The immune biomarkers were collected according to the WBC count. The hematologic parameters required were absolute neutrophil count, absolute monocyte count, absolute lymphocyte count, absolute platelet count, and total WBC count. Immune biomarkers were calculated as ratios: *1)* NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count; *2)* dNLR was determined as the neutrophil count in relation to the WBC count subtracted from the neutrophil count); *3)* PLR was defined as the absolute platelet count divided by the absolute lymphocyte count; and *4)* LMR was established as the absolute lymphocyte count divided by the absolute monocyte count. The primary outcome variable was 5-year OS. Other variables reviewed were stage, margin, and neck management.

The stage was classified according to the eighth edition of the International Union Against Cancer (UICC)[20] and the diagnosis of OSCC was confirmed pathologically.

Margin status was reported by a dedicated pathologist. According to the method of Batsakis,[21] patients were categorized into 3 groups: clear, close, and involved margin. Clear margin referred to no evidence of tumor within 5 mm of the closest point to the surgical resection margin. Close margin alluded to tumor within 5 mm of the margin but without evidence of

tumor at the margin. Involved margin meant evidence of frank tumor at the margin.

Patients underwent surgical options for neck management (elective or therapeutic neck dissection) or watchful waiting with physical and radiologic follow-up. Elective treatment of the neck in patients with early-stage clinically N0 has been historically controversial.[5] Ipsilateral elective neck dissection was performed for stage II. Therapeutic neck dissection was carried out for patients with diagnosed nodal metastasis. Watchful waiting with physical and radiologic follow-up was adopted for patients with OSCC stage I,.

The χ^2 or Mann-Whitney U test was used to compare categorical or continuous variables, respectively. Receiver operating characteristic (ROC) curves were built for each immunologic ratio to ascertain its sensitivity and specificity for the prediction of vital status (alive or dead) at the end of follow-up. Areas under ROC curves (AUC-ROCs) were computed with the trapezoidal rule, and the Youden index (sensitivity + specificity − 1) was used to determine optimal cutoff points.

The Kaplan-Meier estimator was used to calculate 5-year OS (main outcome of the study) and its modulation by comorbidity and immune biomarkers (predictors). Survival differences were compared with the log-rank test. A prognostic multivariate model was built using Cox regression analysis. Data were analyzed using R 3.1.3 (http://www.r-project.org). Level of significance was set at .05.

The Clinical Research Ethics Committee of Aragón approved this study. The Declaration of Helsinki was followed in the present study.

Results

PATIENT CHARACTERISTICS

A total of 215 patients who received surgery under general anesthesia for OSCC were included in this analysis. Patient and tumor characteristics are listed in Table 1. Table 2 presents the study variables segmented by comorbidity groups. The median age of patients at the time of diagnosis was 67.5 years (range, 32 to 95 yr) and most patients were men (67.4%; male-to-female ratio, 2:1). Data retrieved from these patients' clinical records showed that 159 patients (73.9%) presented an associated comorbidity. Forty percent of men and 30% of women were smokers ($P < .001$). Eighty-two men (58%) and 8 women (12%) drank alcohol everyday ($P < .001$). According to the ACE-27 score, those comorbidities were classified as mild (32.1%), moderate (27%), or severe (15%). The total follow-up was 5 years (median, 41 months; range, 7 to 78 months).

Table 1. PATIENTS AND TUMOR CHARACTERISTICS AT TIME OF DIAGNOSIS

Variable	All Patients (N = 215)
Gender	
Men	145 (67)
Women	70 (33)
Age (yr)	67.5 (58.2; 77.4)
Comorbidity	
No or mild comorbidity	125 (58.1)
Moderate to severe comorbidity	90 (41.9)
Stage	
I	98 (45.6)
II	57 (26.5)
III	17 (7.91)
IV	43 (20.0)
Location	
Tongue	74 (34.4)
Floor of mouth	41 (19.1)
Buccal mucosa	18 (8.37)
Retromolar trigone and alveolar ridge	82 (38.1)
Tumor differentiation	
Well	61 (28.4)
Moderate	128 (59.5)
Poor	26 (12.1)
Margins	
Clear margin (≥5 mm)	127 (59.9)
Close (1-4 mm)	57 (26.9)
Positive margins (<1 mm)	28 (13.2)
Management of neck	
Elective node dissection	88 (40.9)
Follow-up	81 (37.7)
Therapeutic node dissection	46 (21.4)
Inflammatory biomarkers	
NLR	2.22 (1.68; 3.29)
dNLR	1.54 (1.21; 2.06)
PLR	104 (78.0; 146)
LMR	3.17 (2.40; 4.20)

Note: Data are presented as median (first quartile; third quartile) or number (percentage).

Abbreviations: dNLR, derived neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Jariod-Ferrer et al. Comorbidities and Overall Survival in OSCC. J Oral Maxillofac Surg 2019.

The most common primary tumor location was the tongue (34.4%), followed by the floor of the mouth (19.9%), and most such tumors were moderately differentiated. Based on the eighth edition of the TNM-UICC and American Joint Committee on Cancer staging system,[20] 155 patients (72%) had early disease (stage I or II), whereas 60 (28%) had locally advanced disease (stage III or IV). Negative margins were present in 127 patients (59.9%) and close and positive margins were observed in 57 and 28 patients, respectively

Table 2. PATIENT AND TUMOR CHARACTERISTICS BY COMORBIDITIES

	No or Mild Comorbidity (n = 125)	Moderate to Severe Comorbidity (n = 90)	*P* Value
Gender			.408
Men	81 (64.8)	64 (71.1)	
Women	44 (35.2)	26 (28.9)	
Age (yr)	65.3 (55.3; 74.0)	71.6 (62.6; 81.7)	<.001
Stage			.742
I	60 (48.0)	38 (42.2)	
II	33 (26.4)	24 (26.7)	
III	10 (8.00)	7 (7.78)	
IV	22 (17.6)	21 (23.3)	
Location			.873
Tongue	44 (35.2)	30 (33.3)	
Floor of mouth	23 (18.4)	18 (20.0)	
Buccal mucosa	9 (7.20)	9 (10.0)	
Retromolar trigone and alveolar ridge	49 (39.2)	33 (36.7)	
Tumor differentiation			.532
Well	34 (27.2)	27 (30.0)	
Moderate	78 (62.4)	50 (55.6)	
Poor	13 (10.4)	13 (14.4)	
Margins			.619
Clear margin (≥5 mm)	76 (61.3)	51 (58.0)	
Close (1-4 mm)	34 (27.4)	23 (26.1)	
Positive margins (<1 mm)	14 (11.3)	14 (15.9)	
Management of neck			.676
Elective node dissection	53 (42.4)	35 (38.9)	
Follow-up	44 (35.2)	37 (41.1)	
Therapeutic node dissection	28 (22.4)	18 (20.0)	
Inflammatory biomarkers			
NLR	2.05 (1.61; 2.96)	2.51 (1.80; 3.71)	.012
dNLR	1.44 (1.13; 1.94)	1.71 (1.37; 2.38)	.006
PLR	98.3 (72.2; 130)	108 (81.9; 148)	.028
LMR	3.40 (2.67; 4.29)	2.85 (2.12; 3.80)	.007

Note: Data are presented as median (first quartile; third quartile) or number (percentage). *P* values indicate statistical difference.

Abbreviations: dNLR, derived neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Jariod-Ferrer et al. Comorbidities and Overall Survival in OSCC. J Oral Maxillofac Surg 2019.

(26.9 and 13.2%). A larger percentage (62.3%) of patients underwent elective or therapeutic neck surgery and then watchful follow-up with physical and radiologic examinations. Median values for NLR, dNLR, PLR, and LMR were 2.22, 1.54, 104, and 3.17, respectively.

ROC CURVES AND CUTOFF POINTS FOR IMMUNE BIOMARKERS

Figure 1 shows ROC curves plotting the sensitivity and specificity for different cutoff points of immune biomarkers. The AUC-ROCs were 64.4, 61.4, 77.3, and 56.2% for the prediction of OS based on the presurgical evaluation of NLR, dNLR, LMR, and PLR, respectively. Next, specificity and sensitivity were balanced to calculate the optimal threshold values to predict OS. Those cutoff points were 3, 1.9, 2.6, and 66 for NLR, dNLR, LMR, and PLR, respectively.

SURVIVAL ANALYSIS

During 5 years of follow-up (median, 31 months; range, 7 to 78 months), the 1-, 3-, and 5-year OSs for the cohort were 88, 68, and 57%, respectively. Death from any cause was observed in 74 patients (34%); 43 died of cancer-specific causes (20%) and 30 died of intercurrent disease (14%). During this period, 141 patients (66%) presented recurrences, with local recurrence being the most frequent (13%). Adjuvant therapy was administered to 49 patients (23%): 28 patients (13%) were treated with radiotherapy after

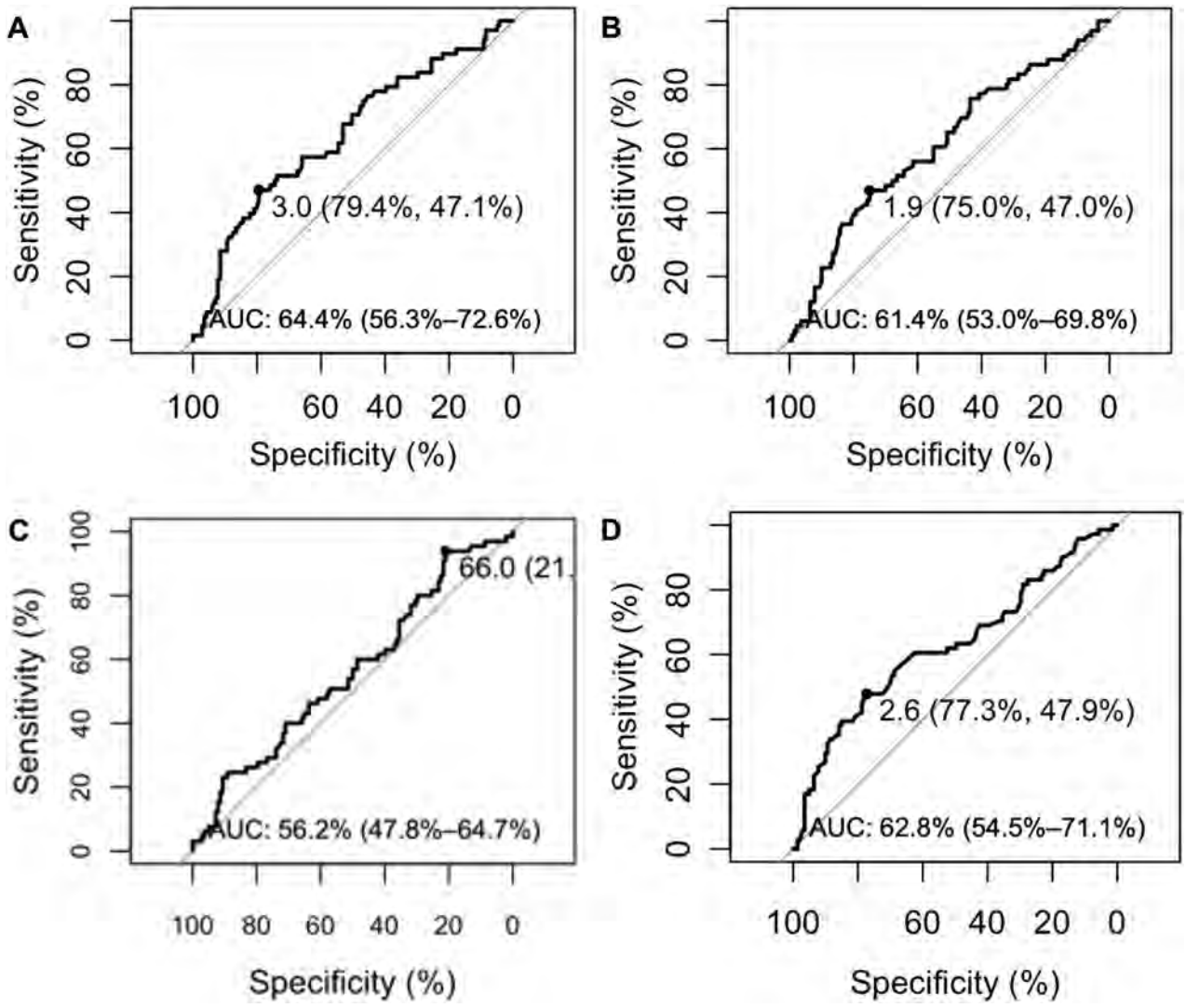

FIGURE 1. *A,* Receiver operating characteristic curve for neutrophil-to-lymphocyte ratio. *B,* Receiver operating characteristic curve for derived neutrophil-to-lymphocyte ratio. *C,* Receiver operating characteristic curve for platelet-to-lymphocyte ratio. *D,* Receiver operating characteristic curve for lymphocyte-to-monocyte ratio. *A-D,* AUCs with confidence intervals and optimal cutoff points according to the Youden index are displayed. AUC, area under the receiver operating characteristic curve.

Jariod-Ferrer et al. Comorbidities and Overall Survival in OSCC. J Oral Maxillofac Surg 2019.

the surgery and 21 (10%) were treated with chemotherapy plus radiotherapy.

Comorbidity had a relevant effect on survival because patients showed considerably worse survival with increasing ACE-27 score (Fig 2). Next, cutoff points were calculated to stratify patients and then Kaplan-Meier analysis was performed (Fig 3). NLR, dNLR, LMR, and PLR were associated with OS ($P \leq .001$, $P = .001$, $P \leq .001$, and $P = .0079$ by log-rank test, respectively; Fig 3A-D). Table 3 presents the strength of the association between the study variables and 5-year OS.

Age, comorbidity, stage, margins, management of the neck, and immune biomarkers were evaluated in a multivariate Cox regression model. This analysis showed that age, moderate and severe comorbidity, tumor stage, margins, and management of the neck were relevant independent predictors of decreased OS (Table 4). PLR (≥66) also was marginally associated with an approximately 4-fold increase of all-cause mortality ($P = .059$)

Discussion

In the present study, comorbidity was the clinical parameter most meaningfully related to OS. The prognostic capacity of comorbidity at the time of diagnosis depended mainly on the different comorbid organ system ailments classified as moderate or severe comorbidity. Likewise, some immune biomarkers were

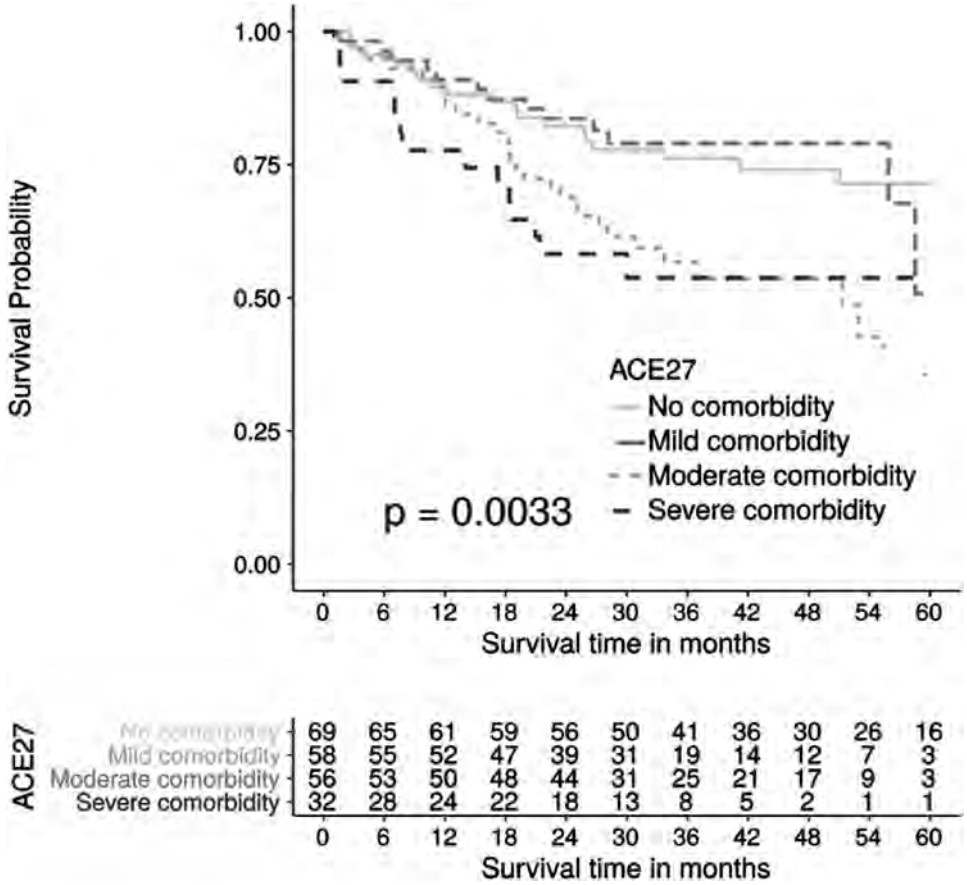

FIGURE 2. Survival curves according to the ACE27 in the 3-category severity system (mild, moderate, and severe) for the number of patients at risk at the beginning of the study versus the number alive at the end of the study. ACE27, Adult Comorbidity Evaluation–27.

Jariod-Ferrer et al. Comorbidities and Overall Survival in OSCC. J Oral Maxillofac Surg 2019.

related to OS in bivariate analyses. However, only PLR was marginally associated with death in the multivariate analysis when all predictor variables were simultaneously taken into account.

Previous studies have shown a noteworthy association between decreased OS and comorbidity in head and neck squamous cell carcinoma and OSCC.[9,22] The present study showed a relevant relation between OS and comorbidity only in patients with moderate and severe comorbidity. The present patients presented increased comorbidities compared with those in other studies, reflecting the health-related problems of this cohort. However, despite this increased prevalence of overall comorbidity, 42% of patients had moderate or severe comorbidity at the time of diagnosis. This percentage was somewhat larger than that reported by Piccirillo and Costas,[23] although a similar prevalence of comorbidity was reported by Ankola et al[22] who studied patients with head and neck cancer using the ACE-27 index and by Singh et al[24] in patients with head and neck cancer graded by the Kaplan-Feinstein comorbidity index. Therefore, the present data confirm that almost half the patients with OSCC present serious health problems that compromise survival independently of cancer stage at the moment of diagnosis. The present study is the first to collect information on resectable OSCC-associated comorbidity in Spain.

It is widely accepted that cancer is related to inflammation and OSCC is one of the most immunogenic tumors, as reported by Ock et al.[25] Tsai et al[26] showed that pretreatment circulating monocyte count was an independent prognostic factor for survival in oral cancer. The present study showed that the NLR, dNLR, PLR, and LMR in the peripheral blood of patients with OSCC at the time of diagnosis and before surgical treatment were strongly associated with OS in the univariate study. Proctor et al[27] found that the NLR and dNLR had similar prognostic value. However, in the present study, dNLR had a slightly decreased prognostic value because it presented a smaller AUC-ROC for the prediction of OS. In line with these results, Rassouli et al[17] reported that a higher pretreatment NLR (>4.27) was associated with higher rates of recurrence

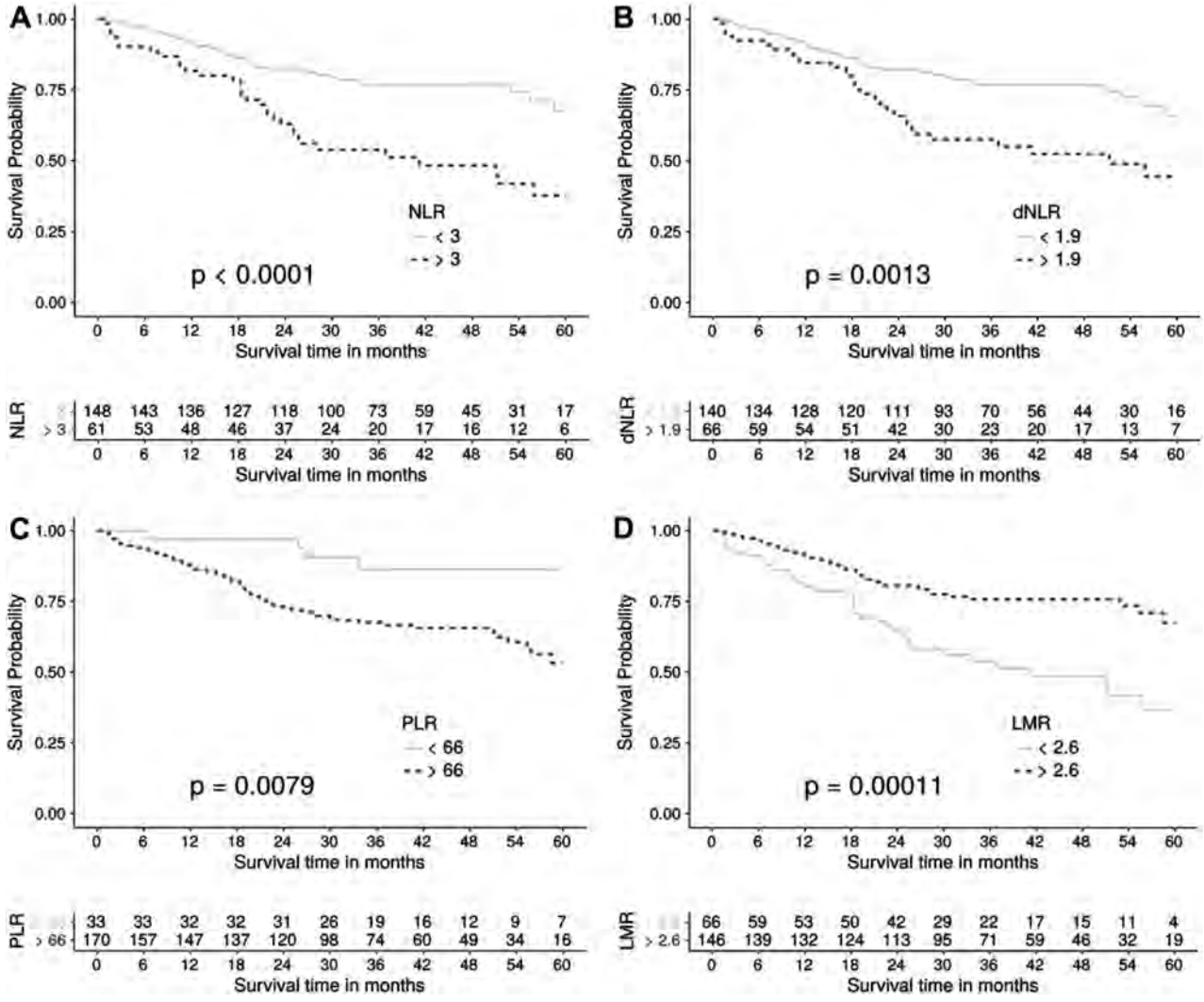

FIGURE 3. *A,* Survival curves for NLR according to the cutoff point calculated in the sample (Fig 1A). *B,* Survival curves for dNLR according to the cutoff point calculated in the sample (Fig 1B). *C,* Survival curves for dNLR according to the cutoff point calculated in the sample (Fig 1C). *D,* Survival curves for LMR according to the cutoff point calculated in the sample (Fig 1D). *A-D,* Curves shows the number of patients at risk at the beginning of the study versus the number alive at the end of follow-up. dNLR, derived neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Jariod-Ferrer et al. Comorbidities and Overall Survival in OSCC. J Oral Maxillofac Surg 2019.

(35 vs 7%; $P < .0001$) and that a higher pretreatment PLR was associated with decreased survival.

In the multivariate analysis, NLR, dNLR, and LMR were not associated with OS, as were age, comorbidity, stage, margin status, and management of the neck. The reason for only PLR appearing to be close to a prognostic factor in the multivariate analysis is not clear. The authors hypothesize that although lymphocytes are key components of host immunity,[28] platelet count might have better prognostic characteristics related to inflammation. In line with this hypothesis, high platelet count also has been reported as a powerful prognostic indicator in solid tumors.[29] Also, it could be connected to the capacity of creating a thrombus, which involves tumoral cells, and migration outside the blood vessels generating a new tumoral bed.

The most relevant result of this study is the confirmation of the strong prognostic value of comorbidity in a homogeneous cohort of patients affected by OSCC treated by surgery first. The results showed that a severe comorbidity increased the risk of death by 4 times in this cohort. The second important result is the suggestive finding of the prognostic role of immune ratios (NLR, dNLR, PLR, LMR) in OSCC, which allowed an approximate portrait of the immune response landscape created by the tumor presence.

Differences in statistical relevance between studies probably occur from the heterogeneity of patients in

Table 3. UNIVARIATE ANALYSIS USING KAPLAN-MEIER ESTIMATOR COMPARED WITH LOG-RANK TEST FOR PROBABILITY OF 5-YEAR OVERALL SURVIVAL

	Events at Beginning of Study, n	Events (Death) at End of Study, n	*P* Value by Log-Rank Test
Age (>80 yr)	177	48	<.001
Comorbidity			.003
No comorbidities	69	13	
Mild	58	18	
Moderate	56	28	
Severe	32	14	
Stage			<.001
I	98	16	
II	57	16	
III or IV	60	41	
Margins			<.001
Clear	127	33	
Close	57	21	
Involved	28	17	
Management of neck			<.001
Elective neck dissection	88	19	
Therapeutic neck dissection	46	35	
Follow-up	81	19	
Immune biomarkers			
NLR >3	61	36	<.001
dNLR >1.9	66	31	.0.1
PLR >66	170	61	.007
LMR <2.6	146	37	<.001

Abbreviations: dNLR, derived neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Jariod-Ferrer et al. Comorbidities and Overall Survival in OSCC. J Oral Maxillofac Surg 2019.

Table 4. MULTIVARIATE ANALYSIS USING COX PROPORTIONAL HAZARDS MODEL OF PROGNOSTIC FACTORS FOR OVERALL SURVIVAL

	HR	95% CI	*P* Value
Age (>80 yr)	3.84	1.94-7.59	.001
Comorbidity			
No comorbidities	1		
Mild	1.94	0.79-4.79	.148
Moderate	2.36	1.04-5.40	.041
Severe	4.04	1.56-10.49	.004
Stage			
I	1		
II	2.10	0.88-5.00	.095
III or IV	2.90	1.00-8.41	.050
Management of neck			
Elective neck dissection	1		
Follow-up	1.15	0.47-2.79	.763
Therapeutic neck dissection	2.95	1.29-6.72	.010
Margins			
Negative	1		
Close or positive	1.91	1.07-3.41	.028
Immune biomarkers			
NLR >3	1.21	0.40-3.63	.735
dNLR >1.9	0.845	0.31-2.31	.743
PLR >66	4.06	0.95-17.42	.059
LMR <2.6	1.04	0.54-2.00	.905

Abbreviations: CI, confidence interval; dNLR, derived neutrophil-to-lymphocyte ratio; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Jariod-Ferrer et al. Comorbidities and Overall Survival in OSCC. J Oral Maxillofac Surg 2019.

terms of ethnicity, tumor site and stage, and geographic differences. Therefore, prospective and multicentric studies are needed to find the accurate relation between systemic immune biomarkers and the outcome of patients with OSCC.

A limitation of the present work is the small sample of patients with OSCC, which warrants further validation in a larger cohort. Intratumoral cell populations were not identified as predictors of survival to focus in clinical prognostic factors. A subsequent study is needed to link intratumoral cell populations, pretreatment WBC count, and OS. The strength of this study is its longitudinal analysis, which decreases statistical type I error compared with single cross-sectional analyses and supports a cause-and-effect relation.

Thus, based on these results, the authors strongly believe that immune ratios and comorbidity should be measured in patients diagnosed with OSCC and should be considered at the time of staging the patient with OSCC. Further studies are warranted to test whether these inexpensive new biomarkers might assist the more classic prognostic factors to maximize their predictive value.

According to the present results, the authors suggest that comorbidity and NLR, dNLR, PLR, and LMR are associated with 5-year OS in patients with resectable OSCC. These results indicate that severe comorbidity in patients with resectable OSCC increases the risk of death by 4 times independently of stage.

Acknowledgments

The authors acknowledge the Miguel Servet University Hospital and all the patients who were treated.

References

1. Amit M, Yen TC, Liao CT, et al: Improvement in survival of patients with oral cavity squamous cell carcinoma: An international collaborative study. Cancer 119:4242, 2013
2. Siegel R, Ward E, Brawley O, Jemal A: Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61:212, 2011

3. Kruaysawat W, Aekplakorn W, Chapman RS: Survival time and prognostic factors of oral cancer in Ubon Ratchathani Cancer Center. J Med Assoc Thai 93:278, 2010
4. van Dijk BA, Brands MT, Geurts SM, et al: Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. Int J Cancer 139:574, 2016
5. d'Alessandro AF, Pinto FR, Lin CS, et al: Oral cavity squamous cell carcinoma: Factors related to occult lymph node metastasis. Braz J Otorhinolaryngol 81:248, 2015
6. Koo K, Harris R, Wiesenfeld D, Iseli TA: A role for panendoscopy? Second primary tumour in early stage squamous cell carcinoma of the oral tongue. J Laryngol Otol 129(suppl 1):S27, 2015
7. Warnakulasuriya S: Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 45:309, 2009
8. Göllnitz I, Inhestern J, Wendt TG, et al: Role of comorbidity on outcome of head and neck cancer: A population-based study in Thuringia, Germany. Cancer Med 5:3260, 2016
9. Piccirillo JF: Importance of comorbidity in head and neck cancer. Laryngoscope 110:593, 2000
10. Sanabria A, Carvalho AL, Melo RL, et al: Predictive factors for complications in elderly patients who underwent head and neck oncologic surgery. Head Neck 30:170, 2008
11. Borggreven PA, Verdonck-de Leeuw I, Rinkel RN, et al: Swallowing after major surgery of the oral cavity or oropharynx: A prospective and longitudinal assessment of patients treated by microvascular soft tissue reconstruction. Head Neck 29:638, 2007
12. El-Deiry MW, Futran ND, McDowell JA, et al: Influences and predictors of long-term quality of life in head and neck cancer survivors. Arch Otolaryngol Head Neck Surg 135:380, 2009
13. Templeton AJ, McNamara MG, Šeruga B, et al: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. J Natl Cancer Inst 106:dju124, 2014
14. Cairns RA, Harris IS, Mak TW: Regulation of cancer cell metabolism. Nat Rev Cancer 11:85, 2011
15. Kuss I, Hathaway B, Ferris RL, et al: Decreased absolute counts of T lymphocyte subsets and their relation to disease in squamous cell carcinoma of the head and neck. Clin Cancer Res 10:3755, 2004
16. Deng Q, He B, Liu X, et al: Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. J Transl Med 13:66, 2015
17. Rassouli A, Saliba J, Castano R, et al: Systemic inflammatory markers as independent prognosticators of head and neck squamous cell carcinoma. Head Neck 37:103, 2015
18. Nishijima TF, Muss HB, Shachar SS, et al: Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: A systematic review and meta-analysis. Cancer Treat Rev 41:971, 2015
19. Paleri V, Wight RG: Applicability of the Adult Comorbidity Evaluation-27 and the Charlson indexes to assess comorbidity by notes extraction in a cohort of United Kingdom patients with head and neck cancer: A retrospective study. J Laryngol Otol 113:200, 2002
20. International Union Against Cancer (UICC). TNM Classification of Malignant Tumours (ed 8). Hoboken, NJ, Wiley, 2016
21. Batsakis JG: Surgical excision margins: A pathologist's perspective. Adv Anat Pathol 6:140, 1999
22. Ankola AA, Smith RV, Burk RD, et al: Comorbidity, human papillomavirus infection and head and neck cancer survival in an ethnically diverse population. Oral Oncol 49:911, 2013
23. Piccirillo JF, Costas I: The impact of comorbidity on outcomes. ORL J Otorhinolaryngol Relat Spec 66:180, 2004
24. Singh B, Bhaya M, Zimbler M, et al: Impact of comorbidity on outcome of young patients with head and neck squamous cell carcinoma. Head Neck 20:1, 1998
25. Ock CY, Keam B, Kim S, et al: Pan-cancer immunogenomic perspective on the tumor microenvironment based on PD-L1 and CD8 T-cell infiltration. Clin Cancer Res 22:2261, 2016
26. Tsai YD, Wang CP, Chen CY, et al: Pretreatment circulating monocyte count associated with poor prognosis in patients with oral cavity cancer. Head Neck 36:947, 2014
27. Proctor MJ, McMillan DC, Morrison DS, et al: A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer 107:695, 2012
28. Watanabe R, Tomita N, Itabashi M, et al: Peripheral blood absolute lymphocyte/monocyte ratio as a useful prognostic factor in diffuse large B-cell lymphoma in the rituximab era. Eur J Haematol 92:204, 2014
29. Barber EL, Boggess JF, Van Le L, et al: Association of preoperative thrombocytosis and leukocytosis with postoperative morbidity and mortality among patients with ovarian cancer. Obstet Gynecol 126:1191, 2015