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The aspartate aminotransaminase/alanine aminotransaminase (De Ritis) ratio predicts sensitivity to radiotherapy in head and neck carcinoma patients

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Abstract

Background: The aim of this study is to evaluate the relationship between the aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) ratio and local disease control in patients with head and neck squamous cell carcinomas (HNSCC) treated with radiotherapy/chemoradiotherapy.

Methods: We calculated the pre-treatment AST/ALT ratio in 670 patients with HNSCC treated with radiotherapy ($n = 309$, 46.1%) or chemoradiotherapy ($n = 361$, 53.9%).

Results: Five-year local recurrence-free survival for patients with a low AST/ALT ratio value ($n = 529$, 79.0%) was 75.0% (95% CI: 71.1–78.9), and for patients with a high value ($n = 141$, 21.0%) it was 53.4% (CI 95: 44.4–62.4) ($p = 0.0001$). In a multivariable analysis, patients with a high ratio had nearly twice the risk of having a local tumor recurrence (HR 1.97, 95% CI 1.42–2.75, $p = 0.0001$).

Conclusion: The AST/ALT ratio was independently associated with the risk of local recurrence in patients with HNSCC treated with radiotherapy or chemoradiotherapy.

KEYWORDS

alanine aminotransaminase, aspartate aminotransaminase, AST/ALT (DeRitis) ratio, prognostic factor, radiotherapy

1 | INTRODUCTION

Several studies have found a relationship between commonly used blood-based parameters and prognosis in patients with head and neck squamous cell carcinomas (HNSCC). Some of these parameters include the neutrophil-to-lymphocyte ratio,[1] the systemic inflammation response index (SIRI), based on a combined analysis

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of the neutrophils, monocytes and lymphocytes count,[2] or the Glasgow prognostic score, that includes the C-reactive protein level to reflect the systemic inflammation status and the serum albumin level to reflect nutritional status.[3] To have markers with prognostic capacity readily available from a simple peripheral blood test makes them attractive parameters to be used for better individualized risk evaluation.

Pre-treatment assessment of patients with HNSCC often includes the study of liver function, with a determination of plasma levels of aminotransaminases, such as aspartate aminotransaminase (AST), also known as glutamic oxaloacetic transaminase (GOT), and alanine aminotransaminase (ALT), also known as serum glutamate-pyruvate transaminase (GPT).

ALT is an enzyme that is mainly located in the liver and catalyzes the transfer of an amino group from alanine to α-ketoglutaric acid resulting in pyruvate and glutamate, while AST is found in several tissues, including the liver, heart, and muscle tissue, and its main function is to participate in the process of aerobic glycolysis within the mitochondria. This enzymatic activity is particularly important in the liver and muscle, but also in other cells with high metabolic activity.

The De Ritis ratio is the proportion of serum AST to ALT levels, which was described by De Ritis et al in 1957.[4] It is used to differentiate varying causes of liver disease. Bezan et al[5] found that a high value of AST/ALT ratio was associated with a decrease in overall survival and metastasis-free survival in patients with non-metastatic renal cell carcinoma. Since then, several authors have found a relationship between an elevated AST/ALT ratio and a poorer prognosis in patients with hepatocellular,[6] bladder,[7] testicular,[8] prostate,[9] or pancreatic[10] carcinomas, including HNSCC.[11,12,13]

The aim of this study is to evaluate the relationship between AST/ALT ratio and local disease control and survival in a cohort of patients with HNSCC treated with radiotherapy.

2 | MATERIAL AND METHODS

2.1 | Patients

Clinical data were obtained retrospectively from a database that prospectively collects information on the clinical characteristics, treatment, and follow-up of all patients with HNSCC treated at our center since 1985.[14] The present study was conducted on a cohort of 771 patients with a histologically confirmed HNSCC treated with radiotherapy during the period between 2000 and 2017 with a minimum follow-up of 2 years. Hematological parameters were collected retrospectively. We included in the study only those patients with a measure of the plasmatic levels of AST and ALT obtained within 3 weeks prior of starting treatment with radiotherapy. According to the reference values of our laboratory, the upper limit of AST and ALT levels was 37 and 41 U/L, respectively. A total of 670 patients met the inclusion criteria. The most common cause of exclusion was a lack of pre-treatment transaminases determination. Table 1 shows the characteristics of the patients included in the study.

All patients were assessed by an Oncologic Board that carried out tumor staging and treatment assignment according to institutional clinical guidelines. Clinical tumor staging was recorded in accordance with the current edition of the TNM at the time of diagnosis.

Treatment with radiotherapy consisted of the administration of a total dose of 70–72 Gy on the primary tumor, 50 Gy on nodal areas at risk in cN0 patients, and 70–72 Gy on nodal areas for cN+ patients. Most patients were treated with the standard regimen (2 Gy/fraction, 1 fraction/day, 5 fractions/week). Eighty-two (12.2%) patients underwent treatment with hyperfractionated radiotherapy (1.2 Gy/fraction, 2 fractions/day, 5 fractions/week). There were modifications in the radiotherapy technique over the period of study. The irradiation was carried out with a linear accelerator with 3D conformation up to 2010 ($n = 422$, 63.0%), when intensity-modulated radiotherapy (IMRT) took over ($n = 248$, 37.0%). Radiotherapy was performed concomitantly with cisplatin (100 mg/m^2 on days 1, 21, and 43 of radiotherapy) in 252 (37.6%) patients, or carboplatin (1.5 AUC weekly) in 56 (8.4%) patients. Fifty-three (7.9%) patients were treated with bioradiotherapy, receiving cetuximab 400 mg/m^2 on day 1 of the week preceding radiotherapy and a weekly dose of 250 mg/m^2 cetuximab during radiotherapy. During analysis, patients treated with bioradiotherapy were included in the group of patients treated with chemo-radiotherapy. A total of 117 (17.5%) patients with clinical, radiological, or metabolic evidence of residual disease at the nodal level after treatment with radiotherapy or chemo-radiotherapy were treated with uni- or bilateral neck dissections. The neck dissections were performed between 6 and 16 weeks after treatment with radiotherapy (median 9.5 weeks).

Human papilloma virus (HPV) DNA detection and genotyping in patients with an oropharyngeal carcinoma was evaluated retrospectively with the SPF-10 PCR/DEIA/LiPA25 system up to 2012, and with the PCR/CLART HPV2 system by GENOMICA (GENOMICA S.A.U., Madrid, Spain) prospectively thereafter. Immunohistochemical positivity against p16INKa was evaluated for all positive PCR samples. The requirement to consider a p16INKa

TABLE 1 Clinicopathological characteristics of the patients included in the study

		No of patients	%
Age (mean/standard deviation) years		62.0/10.7	
Sex	Male	589	87.9
	Female	81	12.1
Tobacco use	No	65	9.7
	≤20 cigarettes/day	90	13.4
	>20 cigarettes/day	515	76.9
Alcohol use	No	149	22.2
	≤80 g/day	293	43.7
	>80 g/day	228	34.0
Site	Oral cavity	33	4.9
	Oropharynx	232	34.6
	Hypopharynx	86	12.8
	Larynx	319	47.6
cT classification	cT1	143	21.3
	cT2	219	32.7
	cT3	220	32.8
	cT4	88	13.1
cN classification	cN0	319	47.6
	cN1	79	11.8
	cN2	232	34.6
	cN3	40	6.0
Overall stage	I-II	213	31.8
	III-IV	457	68.2
Histological grade	Well differentiated	58	8.7
	Moderately differentiated	530	79.1
	Poorly differentiated	82	12.2
Treatment	Radiotherapy	309	46.1
	Chemoradiotherapy	361	53.9

positive sample was staining of at least 70% of the tumor cells at the nuclear or cytoplasmic level with a moderate or high staining intensity. HPV-positive oropharyngeal carcinomas were those with the presence of viral DNA and immunohistochemical positivity to p16INKa.

Pre-treatment plasma levels of AST and ALT were also available for 285 patients treated with surgery over the same period. Table S1 shows the characteristics of this cohort of patients compared to those treated with radiotherapy. The group of patients treated with surgery had a higher proportion of women, with lower alcohol consumption, a higher proportion of tumors located in the oral cavity and less oropharyngeal tumors, a higher proportion of early-stage tumors, and a higher proportion of well differentiated tumors.

The study was approved by our Institutional Review Board and was carried out in accordance with the principles indicated in the Declaration of Helsinki. Due to the retrospective nature of the study, no formal consent was required.

2.2 | Data analysis

We carry out a determination of the pre-treatment AST/ALT ratio by dividing the plasma AST level by the plasma ALT level. First, we analyzed the relationship between the AST/ALT ratio and clinical variables such as age, sex, history of tobacco and alcohol use, location and extent of the tumor, and tumor grade.

The AST/ALT ratio was categorized using recursive partitioning analysis to obtain the cut-off value with the greatest prognostic capacity, considering local control of the disease after treatment with radiotherapy as the

		AST/ALT ratio	*p*-value
Age	<50 years	0.980	0.027
	50–65 years	1.083	
	>65 years	1.154	
Sex	Male	1.073	0.001
	Female	1.267	
Tobacco use	No	1.102	0.512
	≤20 cigarettes/day	1.154	
	>20 cigarettes/day	1.086	
Alcohol use	No	1.058	0.0001
	≤80 g/day	1.015	
	>80 g/day	1.227	
Site	Oral cavity	1.210	0.008
	Oropharynx	1.158	
	Hypopharynx	1.148	
	Larynx	1.026	
Overall stage	I	0.962	0.001
	II	1.064	
	III	1.053	
	IV	1.177	
Histological grade	Well differentiated	0.972	0.030
	Moderately differentiated	1.094	
	Poorly differentiated	1.204	
Treatment	Radiotherapy	1.047	0.021
	Chemoradiotherapy	1.139	

TABLE 2 Average aspartate aminotransaminase/alanine aminotransaminase (AST/ALT) ratio values according to clinicopathological characteristics

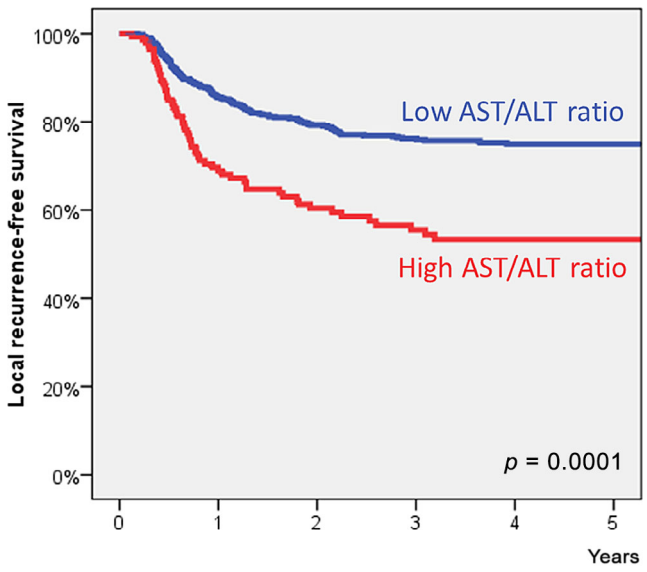

FIGURE 1 Local recurrence-free survival according to the aspartate aminotransaminase/alanine aminotransaminase (AST/ALT) ratio category [Color figure can be viewed at wileyonlinelibrary.com]

dependent variable. Local recurrence-free survival and disease-specific survival were analyzed according to the AST/ALT ratio categories. In addition, the prognostic capacity of the AST/ALT ratio was analyzed stratifying patients according to the primary location of the tumor, the category of local extension of the tumor (T1-2 vs. T3-4), and the type of treatment (radiotherapy versus chemoradiotherapy). Multivariable analysis was done considering local recurrence-free survival and disease-specific survival as the dependent variables and including the AST/ALT ratio as one of the independent variables.

Patients treated with surgery were categorized and local recurrence-free survival and disease-specific survival were determined according to the AST/ALT ratio category based on the cut-off value obtained in the cohort of patients treated with radiotherapy.

For patients with oropharyngeal carcinomas, the AST/ALT ratio was compared between HPV positive and HPV negative tumors. Local recurrence-free survival was analyzed as a function of the AST/ALT ratio category depending on the HPV status.

2.3 | Statistical study

We used the Student *t*-test or ANOVA to evaluate the relationship between the AST/ALT ratio and patient characteristics. The recursive partitioning analysis was performed using the CRT (Classification and Regression Tree) method, considering local recurrence-free survival as the dependent variable. Survival curves were estimated with the Kaplan–Meier method, using the log-rank test to compare the curves. For the multivariable analysis, Cox proportional hazards model was used.

3 | RESULTS

The mean AST value of the patients included in the study was 23.2 U/L (standard deviation 20.1 U/L), and the mean ALT value was 24.1 U/L (standard deviation 21.8 U/L). The total number of patients with AST and ALT values above the upper reference limit was 57 (8.5%) and 66 (9.9%) patients, respectively. Table 2 shows the mean values of the AST/ALT ratio according to the clinical characteristics of the patients. We observed an increase in the mean AST/ALT ratio value as the age of the patients increased. Female patients, with high alcohol consumption, with poorly differentiated tumors or who received concomitant chemotherapy had higher mean AST/ALT ratios. In relation to tumor location, patients with tumors located in the larynx had a significantly lower mean AST/ALT ratio. Finally, a progressive increase in the AST/ALT ratio value was observed as the stage of the tumor increased.

The mean value of the AST/ALT ratio in patients who had a local recurrence of the tumor was significantly higher than in patients where the treatment achieved local control of the disease ($p = 0.013$). Figure S1 shows the distribution in the AST/ALT ratio values according to the local control of the tumor.

Considering local control of the tumor after treatment with radiotherapy as dependent variable, the recursive partitioning analysis classified patients in two categories with a AST/ALT ratio cut-off point of 1, 37. Figure 1 shows the local recurrence-free survival curves according to the category of the AST/ALT ratio. Five-year local recurrence-free survival for patients in the low AST/ALT ratio category ($n = 529$, 79.0%) was 75.0% (95% CI: 71.1–78.9), and for patients in the high category ($n = 141$, 21.0%) it was 53.4% (CI 95: 44.4–62.4). There were

TABLE 3 Five-year local recurrence-free survival depending on the category of the aspartate aminotransaminase/alanine aminotransaminase (AST/ALT) ratio according to the location of the primary tumor, the overall stage, and the type of treatment

		AST/ALT ratio	5-year survival (95% CI)	*p*
Site	Oral cavity	≤1.366 ($n = 23$)	54.1% (32.9–75.3)	0.185
		>1.366 ($n = 10$)	0.0% (0)	
	Oropharynx	≤1.366 ($n = 176$)	79.2% (72.9–85.5)	0.0001
		>1.366 ($n = 56$)	56.3% (42.8–69.8)	
	Hypopharynx	≤1.366 ($n = 65$)	72.4% (60.6–84.2)	0.305
		>1.366 ($n = 21$)	60.0% (36.5–83.5)	
	Larynx	≤1.366 ($n = 265$)	74.7% (69.4–80.0)	0.001
		>1.366 ($n = 54$)	52.6% (38.1–67.1)	
Overall stage	I–II	≤1.366 ($n = 178$)	78.9% (72.8–85.0)	0.055
		>1.366 ($n = 35$)	62.9% (46.0–79.8)	
	III–IV	≤1.366 ($n = 351$)	72.8% (67.9–77.7)	0.0001
		>1.366 ($n = 106$)	49.8% (39.2–60.4)	
Treatment	Radiotherapy	≤1.366 ($n = 250$)	76.3% (70.8–81.8)	0.002
		>1.366 ($n = 59$)	52.2% (38.1–66.3)	
	Chemoradiotherapy	≤1.366 ($n = 279$)	73.8% (68.3–79.3)	0.0001
		>1.366 ($n = 82$)	52.1% (40.5–63.7)	
Alcohol use	No or ≤80 g/day	≤1.366 ($n = 371$)	75.5% (71.0–80.0)	0.002
		>1.366 ($n = 71$)	58.6% (46.7–70.5)	
	>80 g/day	≤1.366 ($n = 158$)	73.7% (66.5–80.9)	0.0001
		>1.366 ($n = 702$)	47.1% (33.6–60.6)	

TABLE 4 Multivariable analysis considering local recurrence-free survival as dependent variable

		HR (95% CI)	*p*
Age	<50 years	1	
	50–65 years	0.86 (0.54–1.38)	0.511
	65 > years	0.90 (0.53–1.50)	0.688
Sex	Male	1	
	Female	0.91 (0.56–1.50)	0.732
Tobacco use	No	1	
	≤20 cigarettes/day	0.88 (0.42–1.82)	0.734
	>20 cigarettes/day	1.41 (0.72–2.75)	0.306
Alcohol use	No	1	
	≤80 g/day	0.56 (0.36–0.87)	0.011
	>80 g/day	0.58 (0.35–0.95)	0.031
Site	Oral cavity	1	
	Oropharynx	0.64 (0.35–1.16)	0.142
	Hypopharynx	0.79 (0.40–1.56)	0.509
	Larynx	0.98 (0.52–1.83)	0.962
cT classification	cT1	1	
	cT2	1.53 (0.91–2.58)	0.104
	cT3	2.57 (1.52–4.35)	0.0001
	cT4	6.34 (3.44–11.67)	0.0001
cN classification	cN0	1	
	cN+	1.39 (0.96–2.00)	0.073
Histological grade	Well differentiated	1	
	Moderately differentiated	1.69 (0.85–3.35)	0.133
	Poorly differentiated	1.05 (0.44–2.48)	0.902
Treatment	Radiotherapy	1	
	Chemoradiotherapy	0.66 (0.45–0.096)	0.033
AST/ALT ratio	≤1.366	1	
	>1.366	1.97 (1.42–2.75)	0.0001

Abbreviations: ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CI, confidence interval; HR, hazard ratio.

significant differences in local recurrence-free survival according to the AST/ALT ratio category ($p = 0.0001$).

These differences in local disease control were reflected in the disease-specific survival. The 5-year disease-specific survival for patients with a low AST/ALT ratio category was 74.6% (95% CI: 70.7–78.5), and for patients with a high AST/ALT ratio category it was 56.8% (95% CI: 48.0–65.6) ($p = 0.0001$).

To analyze whether the AST/ALT ratio had prognostic capacity in patients treated with surgery, an analysis was performed classifying the cohort of 285 patients treated with surgery according to the cut-off value obtained in those patients treated with radiotherapy. There were no differences in the values of AST ($p = 0.859$), ALT ($p = 0.951$), or AST/ALT ratio ($p = 0.570$) between patients treated with surgery or radiotherapy. Five-year local recurrence-free survival for patients treated with surgery and an AST/ALT ratio below 1, 37 ($n = 206$, 72.3%) was 82.1% (95% CI: 76.4–87.8), and for patients with an AST/ALT ratio above the cut-off point ($n = 79$, 27.7%) it was 85.3% (95% CI: 77.3–93.3). There was no significant difference in local recurrence-free survival depending on the AST/ALT ratio category in surgically treated patients ($p = 0.804$). Figure S2 shows the local recurrence-free survival depending on the AST/ALT ratio for patients treated with surgery.

For patients treated with radiotherapy, the improvement in local control related to the AST/ALT ratio category was maintained regardless of the location of the

TABLE 5 Results obtained in studies that have analyzed the prognostic capacity of the aspartate aminotransaminase/alanine aminotransaminase ratio in patients with squamous cell carcinoma of the head and neck

Author	Year	Patients	N	% radiotherapy	Cut-off point % low / % high	Results
Takenaka[11]	2016	Head and neck stage IVa	213	75.3	2.3 87.3%/12.7%	OS: HR 2.17 (1.02–4.22, $p = 0.045$)
Wu[12]	2019	Nasopharynx	1023	100	1.65 65.9%/34.1%	DSS: 1.64 (1.25–2.16, $p < 0.001$) PFS: 1.69 (1.30–2.19, $p < 0.001$) OS: 1.81 (1.39–2.40, $p > 0.001$)
Knittelfelder[13]	2020	Oral cavity, oropharynx	515	100 (52.2 postoperative)	1.44 72.4%/27.6%	DSS: 1.64 (1.10–2.43, $p = 0.014$) OS: 1.55 (1.12–2.15, $p = 0.008$)
Current study	2021	Head and neck	670	100	1.366 79.0%/21.0%	LRFS: HR 1.97 (1.42–2.75) DSS: 1.57 (1.12–2.18)

Abbreviations: DSS, disease-specific survival; LRFS, local recurrence-free survival; OS, overall survival; PFS, progression-free survival.

primary tumor, tumor stage or treatment with exclusive radiotherapy or chemoradiotherapy, although the differences in local recurrence-free survival did not reach statistical significance for patients with tumors located in the oral cavity or hypopharynx, and was marginal for patients with early-stage tumors ($p = 0.055$). Given the association observed between high alcohol use and the AST/ALT ratio value, and in order to rule out that an alteration in plasma aminotransferase levels related to alcohol use could bias the results, we calculated the local control of the tumor after treatment with radiotherapy considering patients with no history of moderate alcohol use or with moderate use (≤80 g/day) versus patients with severe alcohol use (>80 g/day). There were significant differences in the local control of the tumor after treatment with radiotherapy independently of alcohol use. Table 3 shows the 5-year local recurrence-free survival according to the category in AST/ALT ratio depending on the primary location of the tumor, tumor stage, type of treatment, or history of alcohol use.

Table 4 shows the result of a multivariable analysis in which local recurrence-free survival was considered the dependent variable. The variables that were independently associated to a decrease in local control were the absence of alcohol use, patients with advanced local extension of the tumor, exclusive treatment with radiotherapy, and a high AST/ALT ratio. In relation to patients in the low AST/ALT ratio category, patients in the high category had almost twice the risk of having a local recurrence of the tumor (HR 1.97, 95% CI 1.42–2.75, $p = 0.0001$).

An additional multivariable analysis was performed considering disease-specific survival as the dependent variable. Table S2 shows the multivariable analysis. In relation to the patients with a low AST/ALT ratio category, patients with a higher AST/ALT ratio had a 1.57 times higher risk of dying as a result of tumor's progression (95% CI: 1.12–2.18, $p = 0.007$).

Information regarding HPV status was available for 145 of the patients with oropharyngeal carcinomas. A total of 44 (30.3%) patients had HPV-positive tumors. There were no significant differences in the AST/ALT ratio value according to HPV status ($p = 0.740$). We analyzed the local disease control according to the AST/ALT ratio category depending on HPV status. Figure S3 shows the local recurrence-free survival curves for patients with oropharyngeal carcinoma as a function of the AST/ALT ratio category depending on the HPV status. HPV-negative patients with high AST/ALT ratio category had significantly lower local disease control than patients with low AST/ALT ratio category (45.2% vs. 72.0, $p = 0.006$). In contrast, no significant differences in local recurrence-free survival as a function of AST/ALT ratio category were seen for patients with HPV-positive oropharyngeal carcinomas (90.9% vs. 85.7%, $p = 0.559$).

4 | DISCUSSION

Since the description by Bezan et al[5] of the relationship between the AST/ALT ratio (De Ritis ratio) and oncological outcomes in patients with renal cell carcinoma, several studies have found that high values of AST/ALT ratio are associated with a decrease in disease control and survival in different tumor types.[6-10] In a pooled analysis of a total of 18 studies that included information from 9400 patients with tumors from different locations, Wu et al[15] estimated that high levels of AST/ALT ratio were associated with a reduction in disease-specific survival (pooled HR: 2. 07, 95% CI: 1.74–2.46, $p < 0.001$), recurrence-free survival (pooled HR = 1.51, 95% CI: 1.15–1.99, $p = 0.003$), and overall survival (pooled HR: 1.70, 95% CI: 1.38–2.09, $p < 0.001$) .

To date, three studies have been published assessing the AST/ALT ratio in patients with HNSCC. Takenaka et al[11] analyzed the prognostic capacity of the AST/ALT ratio in patients with HNSCC from various locations treated preferentially with radiotherapy (75.3% of the total cohort), finding that patients with advanced stage tumors (IVa) with a high AST/ALT ratio had a significant reduction in overall survival.

Wu et al[12] analyzed 1023 patients with nasopharyngeal carcinomas treated with radiotherapy or chemoradiotherapy and found a significant relationship between recurrence-free, disease-specific and overall survival, and a high AST/ALT ratio. According to the results of a multivariable analysis, the risk of recurrence for patients with a high AST/ALT ratio was 1.69 times higher (95% CI: 1.30–2.19, $p < 0.001$) compared to patients with a low AST/ALT ratio.

Finally, Knittelfelder et al[13] studied 515 patients with carcinomas of the oral cavity or oropharynx treated with exclusive radiotherapy or chemoradiotherapy ($n = 246$) or with surgery and adjuvant radiotherapy ($n = 269$). In a multivariable analysis, they found a significant relationship between AST/ALT ratio and disease-specific survival (HR 1.45, 95% CI: 1.12–1.88, $p = 0.005$). Table 5 summarizes the findings of the studies that have assessed the prognostic capacity of the AST/ALT ratio in patients with HNSCC.

According to our results, a high AST/ALT ratio prior to treatment with radiotherapy in patients with HNSCC was associated with a significant increase in the risk of local recurrence, which led to a decrease in disease-specific survival. The results of a multivariable analysis showed that patients with a high AST/ALT ratio had almost twice the risk of developing a local recurrence of the tumor after treatment with radiotherapy. We hypothesize that tumors with a high AST/ALT ratio have reduced sensitivity to radiotherapy.

In patients with oropharyngeal carcinomas, we could see how the relationship between the AST/ALT ratio value and the response to treatment with radiotherapy was only maintained for patients with HPV-negative tumors. This result coincides with Knittelfelder et al,[13] who also found no relationship between AST/ALT ratio and disease control in patients with HPV-positive tumors.

When applying the cut-off point obtained in patients treated with radiotherapy to a cohort of patients treated with surgery, we observed that the AST/ALT ratio did not show predictive capacity. When considering this lack of predictive capacity in surgically treated patients, we should caution that we observed differences between these patients and those treated with radiotherapy. It should be noted that most of the patients included in the previous studies conducted on patients with HNSCC, which in all cases showed a relationship between a high AST/ALT ratio and poor prognosis, were treated with radiotherapy.

A hypothesis that would explain why a high AST/ALT ratio is associated with a lower local tumor control in patients treated with radiotherapy would involve glutamine metabolism. Glutaminolysis takes place in all proliferating cells, especially in tumor cells.[16] Cancer cells exploit glutaminolysis to resupply the tricarboxylic acid cycle (TCA, Krebs cycle) with carbon as α-ketoglutarate (α-KG). Glutaminase (GLS) catalyzes the hydrolysis of glutamine to glutamate.[17] There are three aminotransferase pathways through which glutamate can be transformed to α-KG. These three paths of catalysis are ALT, AST, and phosphoserine aminotransferase 1 (PSAT1), each of which produces a different amino acid byproduct in addition to α-KG. ALT is critical for α-KG generation and therefore for glutamine/glutamate-mediated TCA cycle anaplerosis in colon cancer cells.[18,19] It is reasonable to assume that those tumors in which this process is most activated have higher plasma levels of AST. On the other hand, there is experimental evidence from bladder carcinoma cell lines that links a reduction in ALT levels to increased aggressiveness of the tumor.[20]

The hyperactive metabolism of cancer cells supports their extreme adaptability and plasticity and facilitates resistance to common anticancer therapies. Glutaminase increases intracellular levels of glutamate, and the enzymatic activity of aminotransferases produces α-KG thus leading to enhanced mitochondrial respiration and ATP production. These reactions lead to increased cellular glutathione levels and thus decreased reactive oxygen species (ROS) levels.[21] Inhibiting glutaminolysis pathways can starve cancer cells by blocking the synthesis of glutamate and thus prevent α-KG from feeding the TCA cycle. Noteworthy, it can also decrease depletion of ROS derived from ionizing radiation and then enhancing radiosensitivity.[22] In fact, current therapeutic strategies include aminooxyacetate, an aminotransferase inhibitor, acting through the inhibition of the mTOR pathway.[23]

In summary, our results indicate that the AST/ALT ratio could be a potential biomarker with predictive capacity of response to treatment with radiotherapy. Having a biomarker available from a simple peripheral blood test could be useful to individualize the most appropriate treatment for every HNSCC patient, and it could be readily used and available in all settings at a low cost.

However, our study has inherent limitations since it was conducted at a single institution using data obtained retrospectively. Prospective studies are needed to validate the predictive capacity of response to radiotherapy of the AST/ALT ratio. Furthermore, the optimal cut-off of the

AST/ALT ratio value will also require further external validation.

5 | CONCLUSION

According to our results, the AST/ALT ratio was independently associated to the risk of local recurrence of the tumor in patients with HNSCC treated with radiotherapy or chemoradiotherapy. Patients with a higher AST/ALT ratio had double the risk of local recurrence of the tumor.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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