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CLINICAL STUDY

Elevated pretreatment lactate dehydrogenase and albumin-to-alkaline phosphatase ratio predict poor prognosis and early treatment discontinuation in head and neck cancer patients with preexistent diabetes mellitus

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ABSTRACT
Increased serum lactate dehydrogenase (LDH) activity is considered as a marker of cellular necrosis and serves as a metabolomic diagnostic marker in several types of cancer including head and neck squamous cell carcinoma (HNSCC). LDH, an enzyme involved in the glycolytic cycle, is correlated not only with the activation of oncogenes such as HIF-α and Myc, but also with effects such as tumor proliferation and metastasis. Serum alkaline phosphatase (ALP) is a marker of cell differentiation and tumor induction. Albumin-to-alkaline phosphatase ratio (AAPR) could be an advantageous biomarker due to its easily accessible dynamics and cost-effectiveness. Elevated values of AAPR could be associated with longer overall survival (OS) in cases with solid tumors. Diabetes mellitus (DM) could influence the outcome of patients with HNSCC by contributing to insulin resistance and chronic inflammation, and by being involved in various aspects of carcinogenesis, disease progression and metastasis. However, the use of antihyperglycemic medications (metformin) can have beneficial effects by inhibiting tumor metabolic pathways. The biomarker role of LDH and AAPR in HNSCC patients with DM has been less evaluated. The purpose of the study was to assess the prognostic value of pretreatment serum lactate dehydrogenase (LDH) and albumin-to-alkaline phosphatase ratio (AAPR) in predicting the duration of non-surgical oncological treatment and glycemic control in cases of head and neck cancers patients with DM, including cases selected from the database of the oncology clinic and oncology outpatient clinic of the Craiova County Hospital. Both LDH and AAPR can be used as pre-treatment biomarkers predictive of treatment response, or prognostic tools included in complex multi-parametric models in HNC associated with DM. However, given the impact of short-term glycemic control on the LDH level, it is necessary to evaluate these biomarkers after assessing and controlling for DM, and with the recommended cut-off value set around 0.5. Due to the limited number of cases, it is necessary to validate the results in multicentric trials with a larger number of patients *(Tab. 5, Ref. 50)*. Text in PDF www.elis.sk
KEY WORDS: diabetes mellitus, HNC, LDH, AAPR, biomarkers, predictive, head and neck cancers, lactate dehydrogenase, albumin-to-alkaline phosphatase ratio.

Introduction

Head and neck cancer is the 6th most prevalent malignancy worldwide, 90% being squamous cell carcinomas of the head and neck (HNSCC). Its high recurrence rate, especially in advanced stages, and approximately 450,000 deaths annually make this disease a priority for improving therapeutic results. The identification of predictive and prognostic biomarkers could improve the results of the treatment by modulating the treatment in order to improve the therapeutic ratio. Increased serum lactate dehydrogenase (LDH) activity is considered as a marker of cellular necrosis and serves as a metabolomic diagnostic marker in several types of cancer including HNSCC. Targeting some metabolic pathways, including inhibiting the Warburg effect in tumors, is one of the current strategies in oncology, almost 100 years after the discovery of this phenomenon characterized by increased glucose uptake and preferential production of lactate. LDH, an enzyme involved in the glycolytic cycle, is correlated with the activation of oncogenes such as HIF-α and Myc, but is also associated with effects such as tumor proliferation and metastasis. Serum alkaline phosphatase (ALP) is a marker of cell differentiation and tumor induction. Albumin-to-alkaline phosphatase ratio (AAPR) could be an advantageous biomarker due to its easily accessible dynamics and

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cost-effectiveness. Elevated values of AAPR could be associated with longer OS in cases with solid tumors. DM could influence the outcome of patients with HNSCC by contributing to insulin resistance and chronic inflammation, and by being involved in various aspects of carcinogenesis, disease progression and metastasis. However, the use of antidiabetic medications (metformin) can have beneficial effects by inhibiting tumor metabolic pathways. The biomarker role of LDH and AAPR in HNSCC patients with DM has been less evaluated (1–13).

Purpose of the study

Evaluation of pretreatment LDH and AAPR as prognostic markers predictive of the duration of non-surgical oncological treatment and glycemic control in cases of patients with HNC associated with DM.

Materials and methods

The cases with preexistent DM and diagnosed with HNC between January 2008 and December 2016 were selected from the database of the oncology clinic and the oncology outpatient clinic of the Craiova County Hospital. The follow-up period varied between 24 months and 120 months. The nadir biological values of glycated hemoglobin (HbA1c) and serum lactate dehydrogenase serum LDH were recorded. Albumin-to-alkaline phosphatase ratio was also evaluated using nadir values of the two variables, as recorded at the first admission to the oncology department. The durations of non-surgical treatment (including chemotherapy and radiotherapy) and OS were also evaluated. For the analysis of correlations of the serum LDH with OS, duration of treatment, and Hb1Ac, the Pearson correlation method was used, with calculations done via an online free application. Twenty-three cases that met the inclusion criteria (a pathologically confirmed head and neck cancer and DM diagnosed and treated before admission to the oncology clinic) were identified. Patients with glycemic values suggestive of DM, but who had not been previously evaluated and proposed for specialized treatment were excluded. Seven anatomical subtypes of HNC were identified. Their distribution is shown in Table 1. Most of the cases were locally advanced stages of the disease, with the locations of distant metastases for stage IVB being lung metastases (1 case), and non-loco-regional nodal metastases (1 case) (Tab. 2). All HNC cases associated with type 2 DM were most frequently treated with oral hypoglycemic medications (Tab. 3). Patient survival data were registered in 15 cases (65.2%) with median OS of 9 months (ranging from 8.5 to 14.5 months) in the group of HNC with preexistent diabetes.

Results

The study group yielded an average HbA1c value of 8.45% (5.7 to 13.1%) and a mean serum LDH value of 308.88 IU/L (ranging from 182 to 543). Although correlations of the nadir LDH value with OS, duration of treatment, and HbA1c were suggested, the calculation of the correlation coefficient was hindered by the study's small group size. Consequently, the results should be interpreted within the context of this limitation. The median albumin-to-alkaline phosphatase ratio recorded at 0.026 (ranging from 0.040 to 0.619) revealed a weak negative correlation with OS and a positive correlation with the duration of treatment. It is worth noting that the nearer the value is to zero, the weaker the relationship.

Discussions

Diabetes mellitus (DM) comprises a group of metabolic diseases characterized by sustained hyperglycemia. Its prevalence is on the increase. In 2014, 387 million adults were reported to be diagnosed with DM. The hypothesis of a relationship between type 2 DM and cancer is demonstrated in cancers of the pancreas, bladder, colon, and breast, while in prostate cancer, the risk is considered lower. Also, DM and cancer share common risk factors including obesity, poor diet and physical inactivity, with chronic inflammation, hyperglycemia and hyperinsulinemia serving as a pathophysiological substrate. The insulin/insulin-like growth factor (IGF) axis seems to be involved in processes such as tumor growth, progression, and metastasis. Hyperglycemia is a predisposing factor of cell growth, while chronic inflammation is correlated with apoptosis. In the case of head and neck cancer (HNC), the association with DM is controversial. Stott-Miller et al. reported a weak correlation in a comprehensive analysis of 12 case-control studies encompassing 6,448 cases and 13,747 controls. Interestingly, a positive association was identified solely in case of never-smokers. Another perspective on the association

Tab. 1. Distribution of cases according to anatomical subtypes criteria.

Anatomical site of HNC	Nasopharynx	Oropharynx	Oral cavity	Hypopharynx	Larynx	Salivary glands	Sinonasal
Case numbers /percentage	2/8.7%	4/17.4%	4/17.4%	2/8.7%	6/26%	1/4.45%	6/35%

Tab. 2. HNC TNM staging.

TNM staging	IIB	III	IVA	IVB	UNSTAGED
Case numbers /percent	1/4.35%	3/13%	13/56.5%	2/8.7%	4/17.4%

Tab. 3. Diabetes treatment in HNC.

DM treatment	Unspecified oral antihyperglycemic agents	Metformin	Insulin	Insulin and oral antihyperglycemic agents
Case numbers /percent	10/43.5%	7/30.5%	8/34.8%	1/4.35%

between metabolic diseases and the risk of HNC emerged from a retrospective cohort study conducted in Korea, using Big Data. The study involving 4,575,818 participants aged over 40 years and initially evaluated in 2008, analyzed the HNC incidence until 2019. While the metabolic syndrome itself was not identified as a risk factor, all its components (obesity, dyslipidemia, hypertension and diabetes) were associated with an increased risk of CKD (14–18).

Kuo et al. retrospectively analyzed the impact of DM on the effectiveness of concurrent chemo-radiotherapy (CCRT) in HNC. Out of 556 cases, 15.1% (84 patients) were diagnosed with both DM and HNC. It is worth noting that the older patient category, in whom the association of DM with HNC was significantly more frequent, received a reduced dose of cisplatin. Hematological toxicity, higher treatment-related death rate, infections and weight loss were significantly higher in cases with concurrent DM and HNC. Tseng et al. report 1.47 times higher incidence rates of HNC in cases with newly known DM compared to the control group. The cohort study from Taiwan identifies oral, oropharyngeal and nasopharyngeal cancers as being associated with DM (19–20).

Nguyễn et al. reported altered glucose metabolism and hyperglycemia during chemo-radiotherapy conducted due to HNC, as well as documented the development of DM in 6% of pre-treatment non-diabetic cases. A similar incidence rate of DM development during cisplatin chemotherapy (5%) was reported by Nan et al. in a group of 219 HNC cases treated with induction chemotherapy. Cisplatin is known to be associated with a decrease in insulin secretion and has even been linked to reported cases of hyperosmolar coma. The use of corticosteroids is considered a minor risk factor when administered short-term during cisplatin treatment for antiemetic and anti-inflammatory purposes. Huang et al. highlights the risk of hyperglycemic crisis which can be a life-threatening condition often underestimated in cases treated with cisplatin. The taxanes-platinum-fluorouracil (TPF) regimen is considered superior to monotherapy with platinum salts or platinum doublet in HNC. Also, the TPF regimen is considered less toxic than the historical PF (platinum-fluorouracil) regimen while TPF induction followed by concurrent chemo-radiotherapy (CCRT) is non-inferior to CCRT, potentially reducing the incidence of metastases in high-risk patients. Bernadach et al. reports a response rate of 82% and a toxic deaths rate of 6% associated with the TPF chemotherapy regimen in HNC and identifies DM as a risk factor associated with treatment-related toxicity (21–25).

LDHA and LDHB, two isoenzymes of LDH, are considered a metabolic bridge between stroma and tumor, serving as possible targets in the research of some anticancer therapies. LDH is correlated with glycolysis and mitochondrial deficiency, contributing to the viable maintenance of tumors. Frequently investigated as a predictive marker for the response to oncological treatment, both pre-treatment and dynamic values of lactate dehydrogenase are evaluated. While baseline LDH is considered a predictor of survival after therapy with bevacizumab, anti-vascular endothelial growth factor (VEGF), in colorectal cancer, the rapid dynamics of LDH (characterized by fast decrease compared to baseline values) was associated with favorable survival also in cases of non-small cell lung carcinoma (NSCLC) treated with the antiangiogenic agent bevacizumab. In small cell lung carcinoma (SCLC), higher LDH values were associated with the risk of brain metastasis and reduced survival rates. Elevated levels of LDH were also correlated with an increased risk of death in cases of bone metastases originating from castrate-resistant prostate cancer (CRPC) or breast cancer. In HNC, elevated levels of LDH were correlated with the tumor grade, development of nodal disease, and risk of distant metastases (26–31).

For over 20 years, the increased rate of glycolysis in the tissue has been considered the cause of increased LDH level in HNC (32). The overexpression of LDH in saliva is associated with necrosis and lesions affecting the integrity of the oral mucosa. The study by Mohajertehran et al. which includes 44 HNSCC cases, demonstrates a significantly higher level of LDH in HNSCC cases compared to the control group, but the most significant overexpression of LDH is associated with tongue and lower oral cavity cancers (33). Elevated preoperative level of LDH (>132 IU/L) is considered a marker for better survival in operated laryngeal cancer, establishing the pre-surgery LDH value as an independent prognostic factor in this subtype of HNC (34). LDH5, the major enzyme of LDH and an isoenzyme linked to glycolysis, was associated with distant metastasis-free survival and DFS, along with death events and distant metastases. In the group of patients treated with definitive radiotherapy, LDH5 was correlated with local relapse-free survival and is recognized as a marker of radio-resistance in HNC (35). LDH ≥202 and smoking ≥30 pack-years were identified in a multivariate analysis as independent prognostic factors in oropharyngeal cancers treated with radiotherapy, regardless of the presence of human papillomavirus (HPV) (36). Increased levels of LDH and lower percentage of lymphocytes were identified as predictors for an unfavorable response to therapy with immune checkpoint inhibitors in HNC. In a multivariate analysis conducted on a group of 186 HNC cases treated with immunotherapy, OS and PFS were also correlated with these values as well as with ECOG performance status, p16 and smoking (37). Elevated pretreatment LDH levels were associated with 3- and 5-year OS rates and DFS in hypopharyngeal cancer, along with other additional factors such as age and nodal status (38). A systematic review and meta-analysis evaluating 19 selected articles with 642 HNSCC cases aimed to assess the correlations between LDH and the progression of HNSCC. The salivary levels of LDH in the HNC group were higher than in the control group, as highlighted by the meta-analysis, demonstrating the value of LDH as an accessible and minimally invasive biomarker in HNSCC (39). Interest in LDH as a possible biomarker has been explored in studies encompassing different anatomical locations in the head and neck regions (Tab. 4) (32–39).

In patients with DM, particularly type 2 DM, the LDH level was independent of long-term glycemic control, but could be correlated with short-term variations in glucose levels. LDH values exceeding normal limits (between 140–280 U/L) have been associated with DM (40, 41).

Pretreatment AAPR is considered as another biomarker that could be included in standard monitoring protocols for patients with solid tumors. Analyzing data obtained from 598

Tab. 4. The role of LDH in different anatomical sites of HNC.

Anatomical site of cancer/histology	Number of case	Results/conclusion	Cuoff/median value(s)	Reference
Oropharynx, hypopharynx, and oral cavity	34	Elevated tumor LDH is related to subsequent development of nodal or distant metastases. LDH is not related to T stage or N stage	7,1	Brizel et al., 2001
HNC		Rise in LDH levels is caused by the increased rate of glycolysis.		Yadav et al., 1994
HNSCC	44	Expression of LDH in the saliva is higher compared to the control group		Mohajertehran et al., 2019
Laryngeal squamous cell carcinoma	640	Elevated preoperative LDH is associated with better OS.	132 IU/L	Guo et al., 2020
HNSCC	141	Elevated LDH5 is related to poorer distant metastasis-free survival and DFS in cases treated with postoperative radiotherapy. Elevated LDH5 is related with poorer local relapse-free survival in cases treated with definitive radiotherapy.		Koukourakis et al., 2009
HPV-positive and HPV-negative oropharyngeal squamous cell carcinoma		Smoking ≥30 pack-years and LDH ≥202 is related with poorer OS after definitive radiotherapy.	202	Uehara et al., 2021
HNSCC	186	Elevated LDH and absolute neutrophils lower percentage of lymphocytes correlate with worse OS and PFS for recurrent/metastatic cases treated with immunotherapy.		Pan et al., 2023
Hypopharyngeal Cancer	189	LDH is an independent predictor of DFS and OS.		Wu et al., 2021
HNSCC	642	LDH levels are higher compared to the control group.		Abedi et al., 2023

EGFR-mutated NSCLC patients with stages IIIB–IV treated with first-line tyrosine kinase inhibitor (TKI), Gan et al. reported OS values of 58.2 months vs 36.7 months in patient cohorts with higher or lower pretreatment AAPR values, with cut-off value set at 0.47. A study evaluating the prognostic value of AAPR in a large cohort of 5,978 lung cancer patients from the Danish Lung Cancer Registry identified only the negative dynamics of AAPR as being associated with reduced OS. Using AAPR and LDH cut-off values of 0.36 and 265.5 U/L, respectively, longer OS (13 vs 7 months) was identified in metastatic NSCLC cases with AAPR ≤0.36. Pretreatment AAPR values were also correlated with clinical outcomes for patients with bladder cancer treated with radical cystectomy (42–45).

The prognostic significance of pretreatment AAPR values in locally advanced laryngeal and hypopharyngeal cancers were analyzed in a group of 341 cases, using a cut-off value of 0.4912. Also, a proposed score, including low AAPR, N1–3, age ≥65 years, and positive vascular invasion, with "one" assigned for each of these variables, was analyzed regarding disease-free survival (DFS) and OS. Lower and higher pretreatment AAPR values were associated with DFS of 46.0%, and 71.9%, respectively, and with OS of 69% and 72.6% at 5 years, respectively in a cohort including locally advanced laryngeal and hypopharyngeal cancers. Also, a higher score was associated with lower OS and DSF. The inclusion of pretreatment AAPR values in a risk model score could facilitate patient stratification in order to optimize the multimodal therapeutic approach. The predictability of preoperative AAPR for 5-year OS, cancer-specific survival (CSS) and DFS were assessed using the cut-off value set at 0.51 in locally advanced oral squamous cell carcinoma. In comparison to AAPR<0.51, the pre-operative values of AAPR ≧0.51 were associated with a significantly higher OS (76.1% vs 48.5%), CSS (84.3% vs 66.4%), and DFS (68.9% vs 42.6%). A nomogram that includes both clinical-pathological characteristics and preoperative AAPR could accurately predict 5-year outcomes of locally advanced oral squamous cell carcinoma cases (46, 47). The prognostic value of the AAPR was assessed for a cohort of 342 cases of HNC treated with concurrent chemoradiotherapy. The cut-off value for AAPR was 0.523, and for a median follow-up of 40 months, an AAPR value <0.523 was associated with inferior overall survival (OS) compared to survival values obtained for AAPR≥0.523. Disease stages IVA-B were also associated with inferior OS compared to stages II–III. The study highlights the significance of the prognosticator AAPR, proposing it for evaluation as a stratification criterion for chemoradiotherapy

Tab. 5. The role of AAPR in different anatomical sites of HNC.

Anatomical site of cancer/histology	Number of cases	Results/Conclusion	Cut-off value(s)	Reference
Nasopharyngeal carcinoma	5,951 patients from 20 cohorts	Elevated AAPR was associated with a better OS in several solid tumors including the nasopharynx		Tian et al., 2020
Larynx and hypopharynx	341	5-year DFS for low vs high AAPR is 46.0 vs 71.9%; 5-years OS for low vs high AAPR is 69.0 vs 72.6%	0.4912	Wu et al., 2021
Oral squamous cell carcinoma	250	Preoperative AAPR<0.51 is a negative prognostic factor for OS.	0.51	Tsai et al., 2022
HNC	342	AAPR < 0.523 is related to worse PFS and OS.	0.523	Kim et al., 2023
Nasopharynx	209	AAPR < 0.447 is associated with shorter OS and PFS.	0.447	Nie et al., 2017

treatment in head and neck cancer (HNC) (48). A retrospective analysis of 209 patients with metastatic nasopharyngeal carcinoma treated with cisplatin-based regimens identified an optimal AAPR level of 0.447. Values below this threshold were associated with an increased LDH level, higher Epstein–Barr virus DNA viral load (EBV), but also with a greater number of bone metastases. All AAPR values<0.447 are associated with a reduced OS and PFS. The study proposes AAPR as a prognostic biomarker for patients with nasopharyngeal cancer treated with cisplatin. However, it emphasizes the need for studies to elucidate the pathophysiological mechanisms explaining the correlation of low AAPR with worthened prognosis. It also highlights the need for an external validation for the APR cut-off value (49).

Considering the controversial nature of AAPR's prognostic role in solid cancers, An et al. conducted a comprehensive study involving 7,019 cases from 25 cohorts across 3 databases (Cochrane Library, PubMed, and Web of Science). The conclusion drawn was that a decreased AAPR adversely affects OS and DSF. The study suggests that this inexpensive and convenient marker, derived from liver function, should be considered for evaluation in more homogeneous studies with stringent inclusion criteria and fewer confounding factors (50). While conclusive evidence related to the potential of AAPR as a predictor of outcomes in different solid tumors is emerging, only a limited number of studies have quantified the relationship between AAPR and HNC (Tab. 5) (12, 46–50).

Conclusions

Both LDH and AAPR hold potential as predictive pretreatment biomarkers, indicators of treatment response, or components in complex prognostic multi-parametric models for HNC associated with DM. However, given the impact of short-term glycemic control on the LDH level, it is necessary to evaluate these biomarkers after assessing and controlling for DM. In the evaluation of AAPR in HNC as a biomarker, a cut-off value around 0.5 should be considered. Due to the limited number of cases, it is necessary to validate these results in multicentric trials with a larger number of patients.

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