Original paper

Podoplanin expression in salivary gland carcinomas and its clinical significance. An immunohistochemical study

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Podoplanin (D2-40) is a lymphatic endothelial marker that is considered as a specific marker for lymphatic endothelial cells and lymphangiogenesis in salivary gland carcinomas (SGCs). Aim: the present study aimed to investigate the immunohistochemical expression of podoplanin in SGCs and to correlate its expression with the clinicopathological parameters and patients' survival.

Forty-nine SGC cases were electronically selected. Demographic, clinical, laboratory, and survival data were reviewed and tabulated. Immunohistochemistry was performed using antipodoplanin. Cases were divided into low and high expression based on a scoring system. A score of 0 and 1 was considered low expression, while > 1 was considered high expression.

Podoplanin high expression was seen in 46.9% of cases, and 53.1% of cases showed low expression. Significant statistical associations were seen between podoplanin expression and tumour grade ($p \leq 0.001$), tumour-nodal- metastasis (TNM) stage ($p \leq 0.001$), tumour size ($p \leq 0.001$), nodal metastasis ($p \leq 0.001$), tumour type ($p = 0.03$), prognosis ($p \leq 0.001$), and mortality ($p \leq 0.001$). The overall survival and progression-free survival differed significantly in cases with high and low expression ($p \leq 0.001$).

Podoplanin overexpression might be a significant prognostic indicator for patients with SGCs, implicating that it is a potential therapeutic target to improve survival in these cancer patients.

Key words: salivary gland carcinomas, immunohistochemical, podoplanin, survival.

Introduction

Salivary gland carcinomas (SGCs) represent a diverse group of tumours with different clinical behaviours and morphological patterns. This difference makes their classification, diagnosis, and treatment a major challenge [1, 2]. Also, SGCs have an unpredictable prognosis, so they constitute an important area in the field of oral and maxillofacial pathology [3, 4]. Of all SGCs, mucoepidermoid carcinoma and adenoid cystic carcinoma are the most common malignant salivary gland tumours [4].

TNM classification of SGCs is an important diagnostic and prognostic factor and the final step before discussing any treatment options [5]. The clinicopathological factors of the TNM system include the presence of lymph node and distant metastasis at diagnosis, and they are considered the most po-

tent unfavourable prognostic factors. A better understanding of how the lymphatics grow and develop metastasis in a variety of tumours aids in predicting cell dissemination and avoiding unnecessary overtreatment [5].

The spread of tumour cells through the lymphatics to regional lymph nodes is a significant independent adverse prognostic factor for patients with SGCs. Many studies have reported the role of lymphangiogenesis in the progression of this lesion. However, the association between lymphatic micro vessel density and lymph node metastasis in SGCs is unclear, and information regarding the lymphatic spread is scarce [6].

The presence of positive draining lymph nodes in SGC cases decreases the mean overall survival in these patients by more than 50% [7].

Hence, many researchers are interested in searching for biological markers to predict the biological behaviour of salivary gland tumours [8]. Lymphatic endothelial markers, such as the antibody D2-40, can be used to analyse nodal metastasis [9]. This marker is considered as a specific marker for lymphatic endothelial cells and lymphangiogenesis in many tumours [10].

Therefore, the present study was carried out to investigate the immunohistochemical expression of podoplanin (D2-40) in SGCs and to correlate its expression with the clinic-pathological parameters of the studied cases.

Material and methods

Case reports

The present study was carried out on 49 formalin-fixed, paraffin-embedded tissue blocks of SGC cases: 26 mucoepidermoid carcinoma, 13 adenoid cystic carcinoma, 5 carcinoma ex pleomorphic adenoma, and 5 acinic cell carcinoma, which underwent complete surgical resection and were diagnosed during the period between January 2011 and December 2018. The cases were collected from the Pathology Lab, Oncology Centre, Faculty of Medicine, Mansoura University and the Oral Pathology Department, Faculty of Dentistry, Mansoura University.

As regards the grading of our studied cases, mucoepidermoid carcinoma were classified as either low grade (grade I), intermediate grade (grade II), and high grade (grade III). Adenoid cystic carcinoma grading is based solely on growth pattern, with 3 grades of increasing aggressiveness based on the predominant growth pattern: grade I – tubular, grade II – cribriform, and grade III – solid. Carcinoma ex pleomorphic adenoma with high grade adenocarcinoma, not otherwise specified, and salivary duct carcinoma, being the most common histologic subtype of the carcinomatous component, are considered high grade (grade III) [11].

The clinical staging of the patients was determined according to criteria set in the tumour-node-metastasis (TNM) system [12].

Tumour recurrence and metastasis were confirmed by radiographical and pathological diagnosis.

The follow-up period was 36 months.

Sections of the cases were stained with H&E to confirm the diagnosis of tumours and to reclassify them into their pathological subtypes.

All the available clinical data for the studied cases were collected from patients' registered medical documents in the Pathology Department, Oncology Centre, and Oral Pathology Department regarding the patient age, sex, site of tumour, tumour size, and presence or absence of lymph node metastasis.

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissues were cut into 4-μm sections, mounted on glass slides, and then deparaffinized in graded alcohol. Endogenous peroxidase activity was blocked with 3% H_2O_2 for 20 min. The slides were incubated overnight at 4°C with the primary antibody podoplanin (D2-40) (rabbit polyclonal antibody, concentrated, Chongqing Biopies Co., Ltd, China). The primary antibody binding was detected using peroxidase-labelled secondary antibody and chromogen, diaminobenzidine (Dako EnVision™ Detection Systems, Dako, Denmark) according to the manufacturer's recommendations. Tissue sections were counterstained with haematoxylin. Negative controls were treated using the same procedures but omitting the use of the primary antibody. The staining of adjacent lymphatic endothelial cells within the same sections was used as the positive internal control. Negative controls were prepared by replacing the primary antibodies with non-immune mouse serum, and no reactive products were detected.

Cytoplasmic and/or membrane immunoreactivity were considered to indicate podoplanin expression positivity. All the slides were reviewed independently by 2 pathologists without knowledge of the clinical information of the patients. Scores were based on staining extension: no positive tumour cells, 0; $<$ 10% positive tumour cells, 1; 10–30% positive tumours cells, 2; $>$ 30% positive tumours cells, 3. A score of 0 and 1 was considered low expression, while $>$ 1 was considered high expression [13].

Statistical analysis

Data were analysed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 26). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested

Table I. Correlation between podoplanin expression and patients' characteristics

Patients' characteristics	Study group, $n = 49$
Age/years (%)	
Mean ±SD	53.14 ±15.73
< 60 y (%)	31 (63.3)
≥ 60 y (%)	18 (36.7)
Gender (%)	
Male	31 (63.3)
Female	18 (36.7)
Site (%)	
Parotid	34 (69.4)
Submandibular gland	7 (14.3)
Palate	6 (12.2%)
Tongue	1 (2.0)
Sublingual	1 (2.0)
Grade (%)	
Grade 1	15 (30.6)
Grade 2	7 (14.3)
Grade 3	27 (55.1)
TNM stage (%)	
I	11 (22.4)
II	9 (18.4)
III	12 (24.5)
IV	17 (34.7)
T (%)	
T1	11 (22.4)
T2	15 (30.6)
T3	12 (24.5)
T4	11 (22.4)
N (%)	
N0	30 (61.2)
N1	10 (20.4)
N2	9 (18.4)
Tumour type (%)	
Low-grade MEC	6 (12.2)
Intermediate MEC	1 (2.0)
High-grade MEC	19 (38.8)
Adenoid cystic carcinoma	13 (26.5)
Acinic cell carcinoma	5 (10.2)
Carcinoma ex pleomorphic adenoma	5 (10.2)
Prognosis (%)	
Stationary	35 (71.4)
Recurrent	14 (28.6)
Podoplanin (D2-40) expression (%)	
Low expression	26 (53.1)
High expression	23 (46.9)
Mortality (%)	
Died	27 (55.1)
Survived	22 (44.9)

M – metastasis, MEC – mucoepidermoid carcinoma, N – node, SD – standard deviation, T – tumour, TNM – tumour-node metastasis

using the c^2test, and the Monte Carlo test was used when the expected cell count was less than 5.

Continuous variables were presented as mean ±SD (standard deviation) for normally distributed data. The Kaplan-Meier test was used for survival analysis, and the statistical significance of differences among curves was determined by log-rank test. For all the above-mentioned statistical tests, the threshold of significance was fixed at 5% (p-value), i.e. the results were considered significant when $p \leq 0.05$. The smaller the p-value obtained, the more significant the results.

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Results

The study was applied to 49 cases of different salivary tumours, of which 31 were male and 18 were female patients, with a mean age of 53.14 ±15.73 years, the clinical criteria of whom are presented in Table I. Most of the tumours were in the parotid gland (69.4%); in contrast, the tongue and sublingual gland were the least likely locations for the tumour to arise (2.0%) for both. As regards tumour size, most cases (30.6%) were T2. T3 tumours represented (24.5%) while T1 tumours and T4 tumours represented (22.4%) for both. Among the 49 tumours analysed, 19 cases (38.8%) were high-grade mucoepidermoid carcinoma – the commonest type, followed by 13 cases (26.5%) of adenoid cystic carcinoma, 6 cases (12.2%) of low-grade mucoepidermoid carcinoma, 5 cases (10.2%) of acinic cell carcinoma, 5 cases (10.2%) of carcinoma ex pleomorphic adenoma, and one case (2.0%) of intermediate-grade mucoepidermoid carcinoma. Regarding the grade distribution of the studied cases, 27 (55.1%) were grade III, 15 (30.6%) were grade I, and 7 (14.3%) were grade II. Among the studied cases, 30 (61.2%)

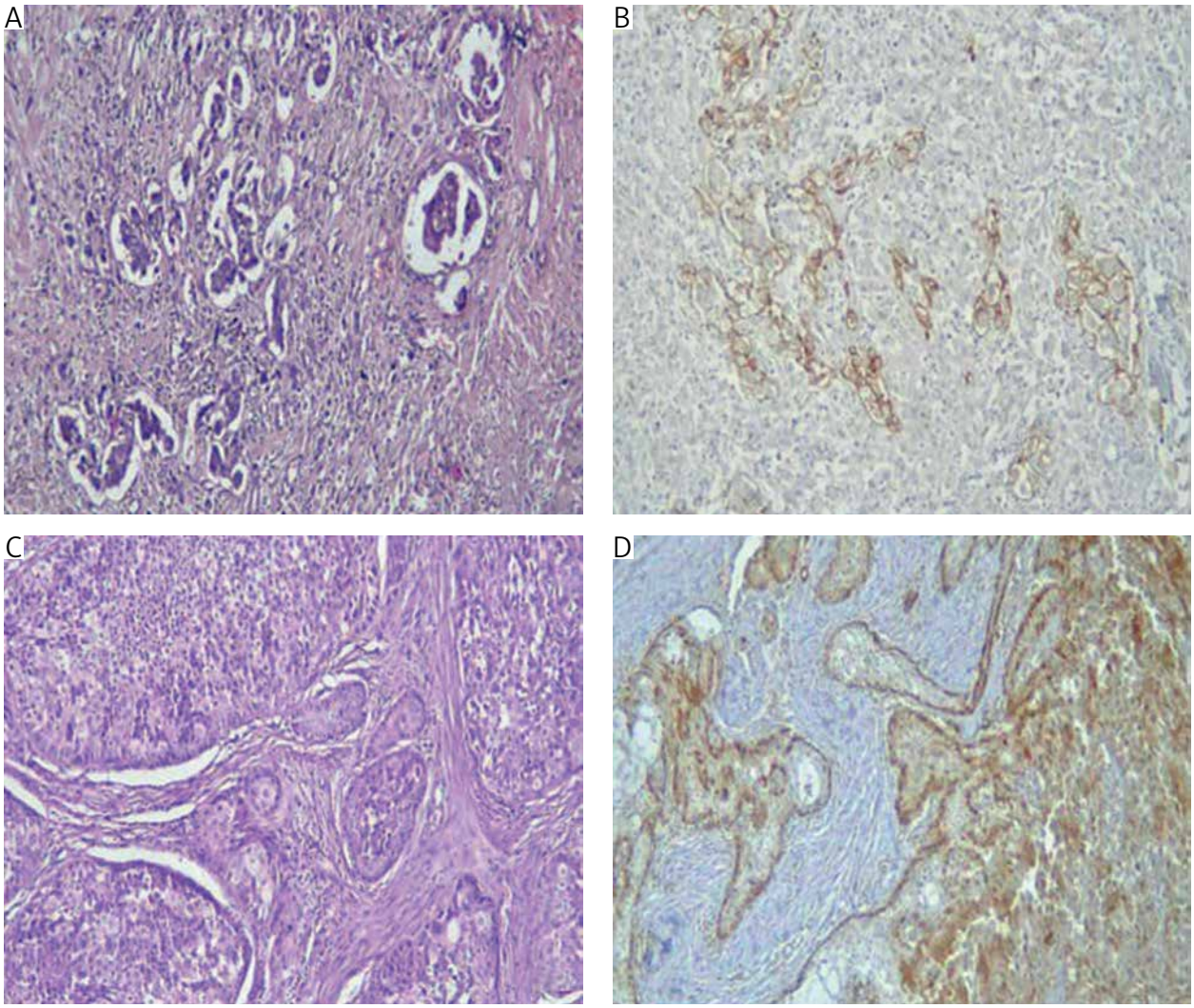

Fig. 1. A) Photomicrograph of high-grade mucoepidermoid carcinoma with frequent lymph vascular tumour emboli (H&E, 200×); B) Previous case that shows immunohistochemical positivity of lymphatic vessel lining for podoplanin (podoplanin 200×); C) Photomicrograph of high-grade mucoepidermoid carcinoma showing solid nests of epidermoid and intermediate cells (H&E 100×); D) Previous case showing cytoplasmic reaction in the tumour cells and at the periphery of the tumour nests (podoplanin 200×)

showed no nodal metastasis. Most of the studied cases were TNM stage IV at diagnosis (34.7%), followed by stage III (24.5%), stage I (22.4%), and stage II (18.4%).

Podoplanin expression and clinicopathological features

Among the 49 tumours analysed, podoplanin expression was low (Fig. 1) in 26 cases (53.1%) while 23 cases (46.9%) showed high expression (Figs. 2, 3). The relationship between podoplanin expression and the clinicopathological parameters is summarized in Table II.

Statistically significant associations were found between podoplanin expression and the following clinicpathological criteria:

- tumour grade ($p \leq 0.001$) – 70.4% of high expression cases were seen in grade 3 tumours, while 81.8% of low expression cases were seen in grade 1 and 2 tumours;
- TNM stage ($p \leq 0.001$) – 79.3% of high expression cases were seen with stage III and IV, in contrast to 100% of low expression cases that were seen in TNM stage I and II;
- tumour size (T) ($p \leq 0.001$) – 78.3% of cases with high expression were in T3 and T4 tumours, in compassion to 80.8% of low expression cases seen in T1 and T2 tumours;
- nodal metastasis (N) ($p \leq 0.001$) – as high expression was seen in 89.5% of cases with nodal metastasis N1 and N2 where 80.0% of low expression cases with no nodal metastasis;
- tumour types ($p = 0.03$) – as 70.0% of cases with high expression were seen in intermediate- and high-grade mucoepidermoid carcinoma, in contrast to 100% of low-expression cases seen in low-grade mucoepidermoid carcinoma;

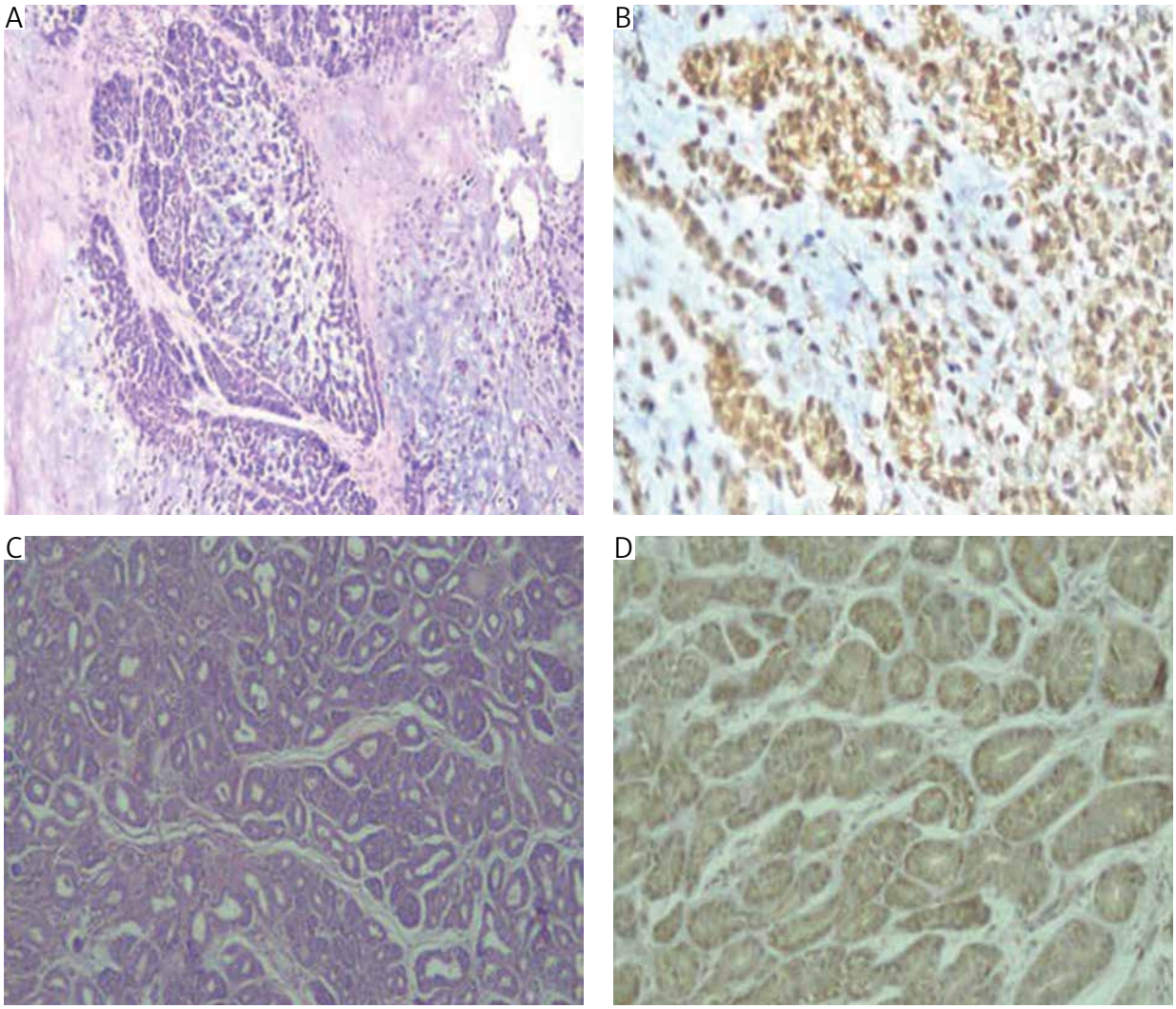

Fig. 2. A) Photomicrograph of not otherwise specified ex PA showing chondroid tissue infiltration by undifferentiated malignant cells (H&E, 200×); B) Previous case showing cytoplasmic reaction in the tumour cells (podoplanin 200×); C) Photomicrograph of adenoid cystic carcinoma with tubular pattern (H&E, 200×); D) Previous case showing cytoplasmic reaction in the basaloid cells (podoplanin 200×)

- prognosis ($p \leq 0.001$) – as 92.9% of high-expression cases were seen in patients who developed recurrence, in contrast (71.4%) to low-expression cases showing stationary clinical course;
- mortality ($p \leq 0.001$) – as 77.8% of patients who died before 36 months were high-expression cases, while only 9.1% of patients survived and 90.9% of low-expression cases survived, in contrast to 22.2% who died.

Podoplanin expression and survival

Clinically, the course of the disease was stationary in 71.4% of patients and showed recurrence in 28.6%. Moreover, 55.1% died before 36 months – the period of follow-up, and 44.9% survived.

As shown in Tables III and IV, the overall survival and progression-free survival,respectively, differed significantly in cases with high and low expression ($p \leq 0.001$). Patients with low podoplanin expression demonstrated both overall survival and progression-free survival advantages contrasting with those with high podoplanin expression (Figs. 4, 5).

Discussion

Cancer has become a heavy burden to health care systems, and it is a leading cause of mortality worldwide [14]. The cure rate of cancer is still relatively low, although diagnostic methods, treatment protocols, and supportive care have improved significantly over the past few decades. This is mainly due to the lack of screening strategies in the early stage and the high recurrence rate of cancer. Targeted therapy, early detection, and early treatment are efficient ways to prevent cancer recurrence. An increasing number of genetic targets are being used to suppress tumours. However, the sensitivity and specificity

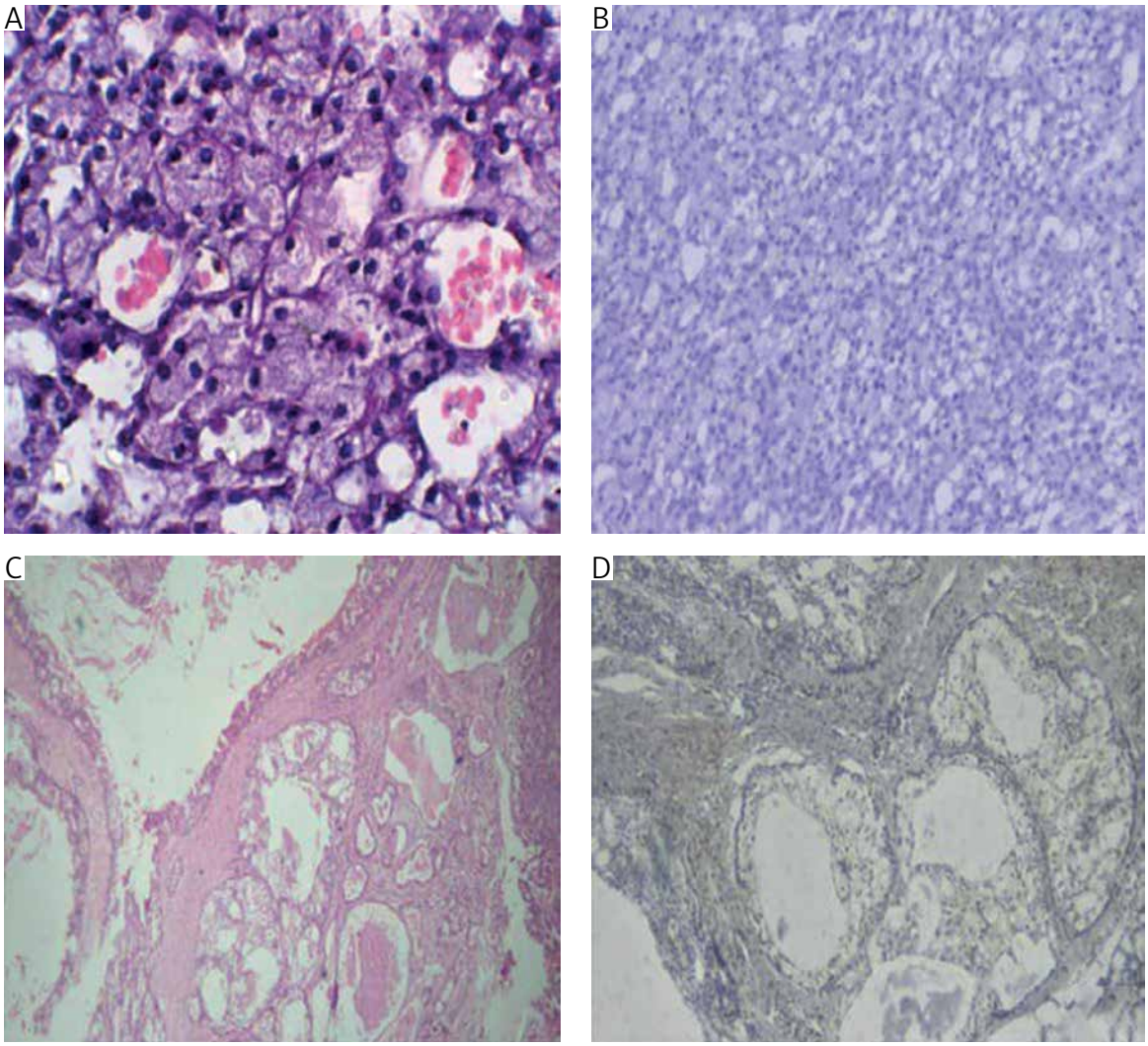

Fig. 3. A) Photomicrograph of ACC showing serous acinar cells with abundant finely vacuolated cytoplasm with basophilic granules (H&E, 400×); B) Previous case showing negative reaction (podoplanin 200×); C) Photomicrograph of low-grade MEC showing numerous cystic spaces (H&E, 100×); D) Previous case showing low expression of podoplanin (podoplanin 100×)

of most of the tumour markers remain controversial. Therefore, it is necessary to discover new genetic targets to prevent tumourigenesis and the development of cancer.

The unpredicted clinical behaviour and prognosis of the malignant salivary gland tumours have raised interest in its study [14]. Therefore, the present study examined the lymphatic density in these tumours for better understanding of the pathogenesis and the clinical behaviour of these tumours.

Podoplanin, a sialomucin-like type 1 transmembrane glycoprotein has been found in a variety of normal tissues, including glomerular podocytes, lymphatic endothelial cells, heart, type I alveolar cells, and skeletal muscle [15–17].

Many studies have proven that podoplanin plays a crucial role in cell motility, organ development, lymphangiogenesis, blood-lymph separation, platelet production, and immune response [18, 19]. However, its physiological functions are still largely unknown. In pathology conditions, a growing body of evidence indicates that it plays an important role in tumourigenesis [20–23]. There is evidence that podoplanin correlates with tumour-associated lymphangiogenesis and cancer-associated fibroblasts [24, 25]. High expression of podoplanin has been observed in various kinds of tumour cells, such as oral cancer, oesophageal cancer, lung cancer, cervical cancer, renal cancer, and cutaneous basal cell carcinoma [26–28]. However, the role of podoplanin in tumour cells remains controversial. In most kinds of cancers, the podoplanin expression is associated with a higher carcinoma cell migration, leading to cancer metastasis, lower survival rates, and poor tumour stage [29–32]. On the other hand, some studies suggest that podoplanin expression is a protective factor in lung and lip carcinoma [33–35]. Thus, it is an important subject that needs to be further explored.

Table II. Correlation between D2-40 (podoplanin) expression and patients' characteristics

Patients' characteristics	Total	Podoplanin (D2-40) expression		χ^2 (*p*-value)
		Low	High	
Age/years (%)				
< 60	31	19 (61.3)	12 (38.7)	2.29 (0.130)
≥ 60	18	7 (38.9)	11 (61.1)	
Gender (%)				
Male	31	18 (58.1)	13 (41.9)	0.848 (0.357)
Female	18	8 (44.4)	10 (55.6)	
Site (%)				
Parotid	34	19 (55.9)	15 (44.1)	MC (0.132)
Submandibular gland	7	2 (28.6)	5 (71.4)	
Palate	6	5 (83.3)	1 (16.7)	
Tongue/sublingual	2	0 (0)	2 (100)	
Grade (%)				13.25 (≤ 0.001*)
Grade 1, 2	22	18 (81.8)	4 (18.2)	
Grade 3	27	8 (29.6)	19 (70.4)	
TNM stage (%)				29.89 (≤ 0.001*)
I and II	20	20 (100)	0 (0)	
III and IV	29	6 (20.7)	23 (79.3)	
T (%)				17.07 (≤ 0.001*)
T1 and T2	27	21 (80.8)	5 (19.2)	
T3 and T4	23	5 (21.7)	18 (78.3)	
N (%)				22.54 (≤ 0.001*)
N0	30	24 (80.0)	6 (20.0)	
N1 and N2	19	2 (10.5)	17 (89.5)	
Tumour type (%)				MC (0.003*)
Low-grade MEC	6	6 (100)	0 (0)	
Intermediate- and high-grade MEC	20	6 (30.0)	14 (70.0)	
Adenoid cystic carcinoma.	13	6 (46.2)	7 (53.8)	
Acinic cell carcinoma.	5	5 (100)	0 (0)	
Carcinoma ex pleomorphic adenoma	5	3 (60.0)	2 (40.0)	
Prognosis (%)				16.59 (≤ 0.001*)
Stationary	35	25 (71.4)	10 (28.6)	
Recurrent	14	1 (7.1)	13 (92.9)	
Mortality (%)				22.96 (≤ 0.001*)
Died	27	6 (22.2)	21 (77.8)	
Survived	22	20 (90.9)	2 (9.1)	

M – metastasis, MEC – mucoepidermoid carcinoma, MC – Monte Carlo test, N – node, SD – standard deviation, T – tumour, TNM – tumour-node metastasis, χ^2 – chi-square test
**significant p ≤ 0.05*

In the present research, the overall expression level of podoplanin in different types of SGCs tumour cells was low in 53.1% of the cases (26 out of 49) and was high in 46.9% (23 out of 49) of the cases.

Most high-grade tumours (grade 3 = 29.6%) showed high expression of the protein, while most of the low-grade tumours (grade 1 and 2 = 81.1%) showed low expression of the protein; this relation was proven to be statistically significant ($p \leq 0.001$).

There is also a significant statistical correlation ($p \leq 0.001$) between the TNM stage and podoplanin expression, because the tumour cells of the advanced

Table III. Kaplan-Meier overall survival

Podoplanin (D2-40) expression	Overall survival				
	Median survival time	Std. error	95% CI	Log rank test	*p*-value
Low expression	32.885	1.570	29.81–35.96	30.36	≤ 0.001
High expression	16.348	2.159	12.11–20.57		
Overall survival	25.122	1.764	21.66–28.57		

CI – confidence interval
**log rank (Mantel-Cox) was used*

Table IV. Kaplan-Meier progression-free survival

Podoplanin (D2-40) expression	Progression-free survival				
	Median survival time	Std. error	95% CI	Log rank test	p-value
Low expression	32.875	1.570	29.79–35.95	31.41	≤ 0.001*
High expression	14.957	2.249	10.54–19.36		
Overall progression-free survival	24.463	1.855	20.82–28.09		

CI – confidence interval
**log rank (Mantel-Cox) was used*

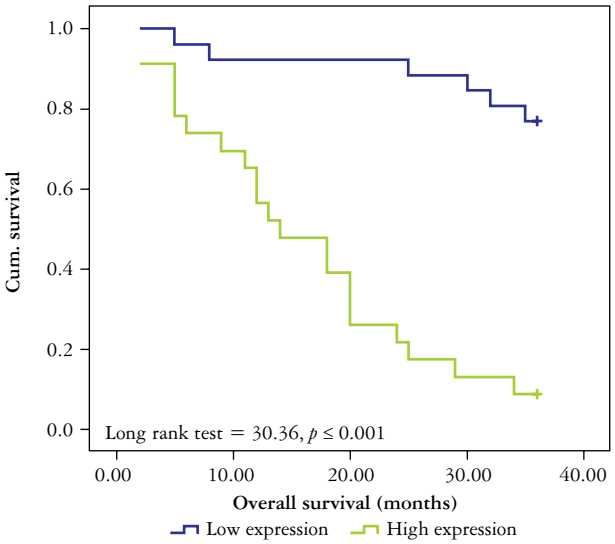

Fig. 4. Kaplan-Meier survival curves for patients with salivary gland carcinomas stratified by podoplanin high or low expression. Overall survival is significantly shorter in patients with high podoplanin expression compared to those with low expression ($p < 0.001$)

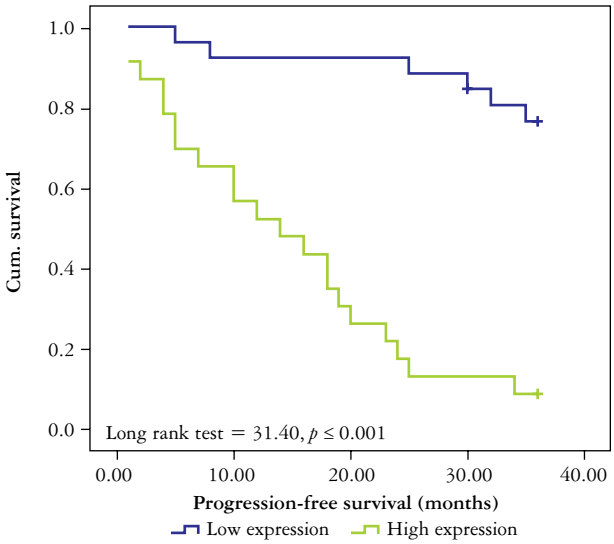

Fig. 5. Kaplan-Meier survival curves for patients with salivary gland carcinomas stratified by podoplanin high or low expression. Progression-free survival is significantly shorter in patients with high podoplanin expression compared to those with low expression ($p < 0.001$)

cases (stages III and IV) showed high expression of the protein in 79.3% of cases versus lower stage cases (stages I and II), which showed lower expression of the protein in 100% of the tumour cells. This highlights the role of podoplanin in facilitating the cancer cells in progression and metastasis. This was proven by the significant statistical correlation between the nodal status of the studied cases and podoplanin expression, because most of the nodal-positive cases (89.5%) showed high expression of podoplanin in their tumour cells, while most of the nodal-negative cases (80%) showed low expression of the protein in the tumour cells ($p \leq 0.001$). This significant correlation between TNM stage and poor N stage with podoplanin expression in tumour cells is in accordance with the results of Wang *et al*. [36] in their meta-analysis on the prognostic value of podoplanin expression in various tumours. This observation stressed the critical role of podoplanin in tumourigenesis by induction of lymphangiogenesis and lymphatic dissemination of the tumour cells. These data suggest the potential use of podoplanin as a molecular marker for distant metastasis in SGCs.

Regarding the correlation between podoplanin expression and histologic subtype of SGCs, this correlation was statically significant ($p = 0.003$). Immu-

nohistochemically, D2-40 showed negative reaction in the acinar cells and positive cytoplasmic reaction in the ductal epithelium of normal salivary gland which was in partial accordance with Wu *et al*. [13], who stated that podoplanin revealed a positive cytoplasmic and/or membrane reaction mainly in myoepithelial cells and different zones of the secretory duct system. Schacht *et al*. [37] stated that D2-40 is expressed in normal human tissue such as kidney podocytes, skeletal muscle, placenta, lung and heart, myoepithelial cell of the breast and salivary glands, osteoblasts, and mesothelial cells.

Lower expression of the protein was noted in all cases of low-grade mucoepidermoid carcinoma (100%), and high expression was observed most of the intermediate- and high-grade mucoepidermoid carcinoma cases (70%).

In high-grade mucoepidermoid carcinoma, podoplanin revealed a cytoplasmic reaction in the tumour cells (epidermoid cells and intermediate cells). Also, lymphatic endothelial cells and at the periphery of the tumour nests showed a podoplanin reaction. These findings were consistent with Gleber-Netto *et al*. [38], who reported cytoplasmic reaction in the neoplastic cells and at the periphery of the tumour nests of mucoepidermoid carcinoma cases. Also, Americo *et al*. [39] stated that podoplanin was used to stain the cytoplasm and cytoplasmatic membrane of lymphatic endothelial cells in mucoepidermoid carcinoma. Dezfuli *et al*. [40] recorded a cytoplasmic reaction in the tumour cells of mucoepidermoid carcinoma cases in their study.

Nearly half of the adenoid cystic carcinoma cases (46.2%) showed lower protein expression, and the other half of the cases (53.8%) showed higher protein expression. This is contradictory to reh results of Wu *et al*. [13], who stated that most of the studied cases of their research on adenoid cystic carcinoma cases showed low expression of podoplanin. This difference could be explained by the variation in the sample size because our work included only 13 cases of adenoid cystic carcinoma versus 40 cases in their study. All cases of acinic cell carcinoma (100%) showed low podoplanin expression. Sixty per cent of carcinoma ex pleomorphic adenoma cases showed high protein expression.

Clinically, the course of the disease was stationary in 71.4% of patients and showed recurrence in 28.6%. Most of the recurrent cases (92.9%) showed high expression of podoplanin, which was significantly higher than the occurrence in the patients with stationary course.

The overall survival and progression-free survival (respectively) differed significantly in cases with high and low expression of podoplanin ($p \leq 0.001$). Patients with low expression demonstrated both overall survival and progression-free survival advantages, contrasting with those with high expression of the protein. Most of the cases who died (77.8%) at the end of the study showed high expression of podoplanin in the tumour cells, while most of the surviving cases (90.9%) showed low podoplanin expression in the tumour cells. This is in accordance with Monteiro *et al*. and Bartuli *et al*. [29, 30], who concluded that podoplanin-positive tumour cells were significantly associated with poor overall survival in both oesophageal carcinoma and oropharyngeal carcinoma. However, there was no significant statistical correlation between its expression and overall survival in lung carcinoma and lip carcinoma [34–35]. This discrepancy in data may be explained by the limited number of eligible studies including survival data for better comparison.

There was no significant difference between the high and low podoplanin expression with respect to age at diagnosis, gender, and tumour site. This is matched with the results of Wang *et al*. [36].

However, further studies with larger sample sizes are needed to validate our findings. Furthermore, the detailed mechanisms underlying the relationship between high podoplanin expression and distant metastasis in SGCs warrant further investigation.

In summary, our results revealed the differential expression of podoplanin among different types of SGCs. There was a significant statistical correlation between podoplanin expression with important prognostic parameters in SGCs, like tumour grade, TNM stage, nodal status, histologic type, recurrence, disease-free survival, and progression-free survival. Further study is needed to elucidate the key role of podoplanin in tumourigenesis and the biological behaviours of the different subtypes of SGCs.

Conclusions

In conclusion, our study suggests that the over-expression of podoplanin might be a significant prognostic indicator for patients with salivary gland cancer, implying that it is a potential therapeutic target to improve survival in these cancer patients. However, more multi-centre clinical investigations with larger sample sizes should be conducted to confirm these findings.

Acknowledgments

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The authors declare no conflict of interest.

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