



BIOMEDICAL SCIENCES

Specific immunohistochemical expression of Mmp-26 in prostatic adenocarcinoma

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Abstract: Matrix metalloproteinases (MMP) have been identified as biomarkers for several diseases, including cancer. The increase in the expression of these enzymes has been related to greater tumor aggressiveness. MMP-26 is expressed constitutively in the endometrium and some cancer cells of epithelial origin. However, there is a lack of studies on its expression on prostatic carcinoma. In this study, the evaluation of MMP-26 reactivity by immunohistochemistry (IHC) was carried out in 150 paraffinized samples representative of benign and malignant prostatic lesions. 70 of the 150 samples showed IHC immunopositivity, being more prevalent in carcinoma cases (44 out of 70 cases) with moderate and strong intensity. The expression and intensity of the MMP-26 reaction showed a significant association with total PSA values. As expected, serum PSA levels were higher in cases of carcinoma than in prostatic hyperplasia or atrophy. Studies have demonstrated the potential of MMP-26 as a tumor marker, and our results have shown that its immunoexpression was useful to differentiate a group of benign and malignant samples in prostate tumors. This characteristic can assist in the predictive assessment and, consequently, in the development of new strategies for the diagnosis, prognosis, and treatment of prostate cancer.

Key words: Immunohistochemistry, metalloproteinase, prostate cancer, PSA.

INTRODUCTION

Prostate cancer (PC) is one of the most prevalent cancers worldwide, ranking second among malignant neoplasms that affect men, behind lung cancer only (Vietri et al. 2021, Noone et al. 2017). PC screening tools include serum prostate-specific antigen (PSA) measurement, rectal examination, and biopsy. Despite its name, PSA has low specificity presenting with high levels in benign conditions such as prostatitis and hyperplasia (HPB), which results in unnecessary treatment and elevated rates of negative biopsy results (El Chaer et al. 2018). Therefore, research of new biomarkers for early, differential diagnosis and with potential for PC prognostic value has been undertaken.

The American Urological Association (AUA) guidelines suggest that PSA levels up to 4 ng/mL are generally considered normal, but this may vary depending on age and other risk factors. PSA levels between 4 and 10 ng/mL are considered a “grey area” where there is an increased risk of prostate cancer, but there may also be other harmless causes for the increase. However, PSA levels above 10 ng/mL are highly suggestive of prostate cancer, but are still inconclusive without a biopsy. Studies have shown that men with PSA levels between 4 and 10 ng/mL had a 25% to 35% chance of having prostate cancer detectable by biopsy, highlighting that even men with $PSA \leq 4.0$ ng/mL can have prostate cancer, although the prevalence is lower (Catalona et al. 1994, Thompson et al. 2004).

Matrix metalloproteinase (MMPs) are endopeptidases that promote degradation and remodeling of the extracellular matrix and play an essential role in various physiological and pathological processes (Almeida et al. 2022). Its exacerbated expression is associated with invasion, angiogenesis, metastasis, and poor prognosis of several types of cancer, such as thyroid (Li et al. 2023), breast (Cid et al. 2018) and prostate (Pouyanfar et al. 2016). MMP-26 is the smallest molecule in the MMP family that was recently discovered. Its constitutive expression was described in the endometrium and placenta, as well as in cancer cells of epithelial origin (Cheng et al. 2017). Its primary substrates include fibronectin, fibrinogen, vitronectin, laminin, and type IV collagen. MMP-26 also can activate pro-MMP-9, known to promote invasion and angiogenesis in several human tumors (Khamis et al. 2013, Wang et al. 2014).

High expression of MMP-26 has been demonstrated in breast, lung, liver, endometrial, ovarian and esophageal cancer cell lines (Lee et al. 2011, Zhao et al. 2015, Yu et al. 2015, Nishi et al. 2013, Ripley et al. 2006, Yamamoto et al. 2004). Nevertheless, research on its role in PC is still scarce. Recently, the prognostic value of MMP-26 has been evaluated in colorectal cancer, where significant expression was associated with invasion, metastasis, and lower overall patient survival (Hu et al. 2014). In PC, its elevation in both serum and tissue levels has revealed its potential as a biomarker (Cheng et al. 2017). Therefore, the objective of this study was to analyze the immunoexpression of MMP-26 in benign and malignant prostatic lesions.

MATERIALS AND METHODS

One hundred and fifty histological samples were obtained from patients presenting with prostatic lesions and treated at the Hospital das

Clínicas da Universidade Federal de Pernambuco (HC/UFPE). The samples were divided into 4 groups, based on its histopathological classification: prostatic atrophy (N = 25), prostatic intraepithelial neoplasia (PIP) (N = 25), benign prostatic hyperplasia (BPH) (N = 50) and prostatic adenocarcinoma (N = 50). Tumor samples in paraffin blocks were obtained from the Pathology Department of the hospital along with their respective clinical reports. Clinical data such as PSA dosage, patient age, and ethnicity were obtained from medical records. The UFPE research ethics board reviewed the protocol and approved the study (approval number CAAE 79701517100005208).

Immunohistochemistry analysis

Blocks containing representative parts of the tumor were subjected to microtomy generating 5µ slices, followed by processing and reactivity. Each slide was deparaffinized in xylol, bathed in decreasing solutions of ethyl alcohol (100%, 100%, and 70%), and deionized water for 5 minutes. After antigenic recovery with citrate buffer (10 mM, pH 6.0) and blocking of endogenous peroxidase and other proteins using the Envision Flex kit (Dako Denmark A / S), samples were incubated with anti-MMP-26 (FNab 05242, Fine Test, 1: 500) in a humid chamber, overnight at 4°C. The material was subsequently immersed in phosphate-buffered saline (PBS, 100 mM, pH 7.2) and incubated with the HRP polymer (Horseradish peroxidase). After PBS wash, the samples were incubated with the Diaminobenzidine developer (DAB), counterstained with hematoxylin, immersed in running water and increasing alcoholic solution (70%, 100%, and 100%) for 5 minutes each. Finally, the slides were immersed in xylol and assembled with coverslips interfaced with synthetic resin. Negative controls were performed using the same protocol in the absence of the primary

antibody. Endometrial adenocarcinoma samples were used for positive controls.

Image collection and analysis

Labeled cells were observed using a Zeiss AxioCam microscope and a Zen Blue image capture system (edition 2011). Manual quantification was used where the parenchymal epithelial cells were evaluated. The reaction was considered as negative when less than four epithelial cells were marked per field, and positive when more than four marked cells were observed per field. The intensity of the reaction was evaluated semiquantitatively according to the reaction in the nucleus or cytoplasm of the cells: weak (04 to 09 nuclei or reactive cytoplasms), moderate (10 to 15 nuclei or reactive cytoplasms) and intense (above 15 nuclei or reactive cytoplasms).

Statistical analysis

Categorical variables were analyzed by the Chi-Square test, the Fisher’s Exact test, and, the Likelihood Ratio Test, according to data distribution. Numerical variables were analyzed with the Kruskal-Wallis test. Positive and negative IHC were compared through the Mann-Whitney test. Statistical significance was judged at the 0.05 level. IMB-SPSS version 23 was used to perform the analyses.

RESULTS

Characteristics of the study population

The study included 150 histological samples obtained from patients with prostatic lesions treated at the Hospital das Clínicas da Universidade Federal de Pernambuco (HC/UFPE). The samples were categorized into four groups based on histopathological classification: prostatic atrophy (N = 25), prostatic intraepithelial neoplasia (PIN) (N = 25),

benign prostatic hyperplasia (BPH) (N = 50), and prostatic adenocarcinoma (PC) (N = 50). Clinical data, including PSA levels, patient age, and ethnicity, were retrieved from medical records. The study protocol was approved by the UFPE research ethics board (approval number CAAE 79701517100005208), (Table I).

Analysis of patients’ PSA levels

Immunohistochemical (IHC) analysis was performed to evaluate MMP-26 expression in the samples. The intensity of the reaction was assessed semi-quantitatively based on the number of reactive nuclei or cytoplasms: weak (4 to 9), moderate (10 to 15), and intense (above 15). The statistical analysis was conducted using Chi-Square, Fisher’s Exact, Likelihood Ratio, Kruskal-Wallis, and Mann-Whitney tests, with significance judged at the 0.05 level (IMB-SPSS version 23), (Table II and III).

Analysis of MMP-26 expression by immunohistochemistry

MMP-26 expression, measured by IHC, was positive in 70 out of the 150 samples (46.7%). The prevalence was highest in the prostate carcinoma (PC) group, with 46 out of 50 cases (92%), followed by the prostatic intraepithelial neoplasia (PIN) group, with 22 out of 25 cases (88%). The benign prostatic hyperplasia (BPH) group showed only 2 out of 50 (4%) positive cases, and the atrophy group showed no reactivity (Figure 1 and 2).

Among the 70 positive samples, weak immunostaining was observed in 34 cases (48.6%), with 22 in the PIN group, 2 in the BPH group, and 10 in the PC group. Moderate reactivity was observed in 31 cases (44.2%) and intense reactivity in 5 cases (7.14%), all in the PC group. The staining pattern was both nuclear and cytoplasmic (Table IV).

Table I. Characteristics of the study population according to histopathological group.

	Group								
Variables (n= 150)	Atrophy (n=25)		NIP (n=25)		HPB (n=50)		ACP (n=50)		p-value
	n	%	n	%	n	%	n	%	
Age group (years)									p ⁽¹⁾ = 0.447
41 a 59 (n=27)	3	12	5	20	12	24	7	14	
60 a 69 (n= 68)	12	48	11	44	17	34	28	56	
70+ (n=55)	10	40	9	36	21	42	15	30	
TOTAL	25	100	25	100	50	100	50	100	
Ethnicity/color									p ⁽²⁾ = 0.010*
White (n=15)	1	4,8	3	17.6	3	7.0	8	27.6	
Brown (n= 66)	9	42.9	9	52.9	30	69.8	18	62.1	
Black (n = 29)	11	52.4	5	29.4	10	23.3	03	10.3	
TOTAL	21	100	17	100	43	100	29	100	
Alcohol consumption									p ⁽¹⁾ = 0.286
Yes (n=44)	7	63.6	3	25.0	17	48.6	17	51.5	
No (n=47)	4	36.4	9	75.0	18	51.4	16	48.5	
TOTAL	11	100	12	100	35	100	33	100	
Smoking									p ⁽¹⁾ = 0.649
Yes (n=49)	9	60	6	42.9	19	50	15	41.7	
No (n=54)	6	40	8	57.1	19	50	21	58.3	
TOTAL	15	100	14	100	38	100	36	100	

(*) Significant difference at the level of 5.0%. (1) Using Pearson’s Chi-square test. (2) Through Fisher’s exact test. In this table, cases without information on each variable were not considered.

For greater precision, we detailed the distribution of immunostaining intensities: Atrophy group**: 0/25 positive cases (0%), PIN group**: 22/25 positive cases (88%), with 22 cases of weak immunostaining, BPH group**: 2/50 positive cases (4%), with 2 cases of weak immunostaining, PCgroup**: 46/50 positive cases (92%), with 10 cases of weak immunostaining, 31 cases of moderate immunostaining, and 5 cases of intense immunostaining. These results indicate a clear predominance of MMP-26 expression in prostate carcinoma samples, with varying intensities of immunostaining that

may reflect different stages or degrees of tumor aggressiveness.

Analysis of the relationship between IHC and PSA

The total PSA levels were significantly different among the groups (p = 0.002). Specifically, PSA levels were categorized as <4 ng/mL, 4-10 ng/mL, and >10 ng/mL. The distribution of PSA levels in relation to IHC results is detailed in Table V. Notably, higher PSA levels were associated with positive MMP-26 expression, particularly in the PC group. Clinical examination revealed

Table II. Results of PSA tests by groups, clinical and histopathological exam.

Variables Exams	Total (n= 150)		Quantity per group								p-Value
			Atrophy (n= 25)		NIP (n= 25)		HPB (n= 50)		ACP (n= 50)		
PSA	n	%	n	%	n	%	n	%	n	%	p ⁽¹⁾ = 0.002*
< 4	37	24.7	06	26.1	06	24	19	47.5	06	12.5	
4 to 10	72	48	16	69.6	14	56	16	40	26	54.2	
> 10	27	18	01	4.3	05	20	05	12.5	16	33.3	
Uninformed	14	9.3									
Clinical exam											
Presence of nodule	36	24									
Absence of nodule	71	47.3									
Uninformed	43	28.7									
Histopathological											
Atrophy	26	17.3									
NIP	10	6.7									
HPB	29	19.3									
ACP	40	26.7									
ASAP	02	1.3									
Others	08	5.3									
Uniformed	35	23.3									

(*) Significant difference at the level of 0.05 (1) Using Pearson’s Chi-square test.

the presence of nodules in 36 out of 107 cases (33.6%), with no significant difference in nodule presence between IHC-positive and IHC-negative groups (p = 0.945). This suggests that while MMP-26 expression correlates with PSA levels, it may not be directly associated with the physical presence of nodules.

DISCUSSION

Since the 1980s, with the introduction of the PSA test in the medical routine, there has been a significant increase in the diagnostic of PC cases and a 20% reduction in the PC mortality rate. Serum PSA is measured for early detection, staging, and monitoring of the disease. However, it might have low specificity when the values range between 3 and 10 ng/ml, and also showing increase in benign conditions such as HPB and prostatitis (Cheng et al. 2017, El Chaer et al. 2018).

The search for new biomarkers, which combined with PSA can provide greater precision in the diagnosis, has led to several studies on the expression of MMP, both in serum and in tissue samples of PC.

Kanoh et al. (2002) and Zhang et al. (2004) observed, high serum levels of MMP-2 and MMP-9 in patients with PC and HPB, with increasing expression as disease progressed. In addition to MMP-2 and -9 Morgia et al. (2005) found that MMP-13 levels were significantly higher levels in patients with PC. MMP-7 was analyzed by Szarvas et al. (2011), and its levels were also strongly elevated, especially in patients with metastatic PC. Riddick et al. (2005) evaluated the expression of MMP-10, -15, -24, -25, and -26, of which MMP-26 was the one showing the highest degree of expression in malignant prostate tissues, strongly correlating with the Gleason score.

Table III. Total PSA, free PSA, and free PSA/total PSA for each group.

Variables	Average ± DP Median (P25; P75)					p-Value
	Total (n=150)	Atrophy (n=25)	NIP (n=25)	HPB (n=50)	ACP (n=50)	
Total PSA (n= 136)						
	10.68 ± 15.37 5.98 (3.85; 9.13)	5.95 ± 3.12 5.70 (3.90; 7.05)	8.22 ± 8.66 5.62 (3.70; 9.62)	8.81 ± 16.79 4.41 (2.13; 7.26)	15.80 ± 18.90 7.93 (5.46; 18.34)	p ⁽¹⁾ = 0.001*
Free PSA (n= 102)						
	1.19 ± 1.13 0.86 (0.50;1.42)	1.05 ± 0.37 0.88 (0.85; 1.43)	1.21 ± 1.36 0.81 (0.40; 1.56)	1.11 ± 1.09 0.82 (0.30; 1.37)	1.30 ± 1.25 0.86 (0.51; 1.74)	p ⁽¹⁾ = 0.628
Free PSA/total PSA (n= 102)						
	17.56 ± 10.29 16.33 (10.30; 23.57)	21.20 ± 6.31 22.03 (16.30; 25.29)	19.29 ± 14.64 14.93 (8.27; 28.64)	19.93 ± 9.71 20.17 (15.25; 23.54)	12.85 ± 7.53 11.02 (8.43; 17.00)	p ⁽¹⁾ = 0.001*

(*) Significant difference at the level of 0.05 (1). Kruskal Wallis test.

Recently, Cheng et al. (2017) observed a marked increase and strong immunoreactivity of MMP-26 in the serum, in PC samples compared to the HPB and control groups. Also, Zhao et al. (2003) noted that MMP-26 was able to activate MMP-9 in PC cells, an essential mechanism in the invasion and metastasis process. An assay with specific inhibitors for MMP-26 generated a reduction in MMP-9 and a significant decrease in the invasive potential of these cells. These findings support the hypothesis that the activation of MMP-9 by MMP-26 may promote an increase in cell invasiveness and, consequently, a worse clinical outcome.

Our results also demonstrated a higher expression of MMP-26 in cases of PC (63%), in addition to a positive association between the IHC expression of MMP-26 with PSA values, what suggests that this enzyme could be used as an adjunct to the measurement of this marker for the differential diagnosis between PC and HPB, as well as for estimating the prognosis of cancer given that it has also showed weak reactivity in NIP samples. The rupture of continuity between

the cell layer and the basement membrane is essential for the progression from intraepithelial neoplasia to prostate carcinoma. Lee et al. (2006) found a higher expression of MMP-26 in cases of PIN compared to PC and that its levels declined in the progression to invasive cancer. His findings suggests that MMP-26 might play an important during tissue transformation between these lesions, serving as an early marker of prostate cancer.

The prognosis of PC is also associated to age, with older age being the best established risk factor. Statistics around the world indicate that both incidence and mortality increase after age 50, with three-quarters of new cases around age 65 (Cheng et al. 2017, El Chaer et al. 2018). Accordingly, we observed that 56% of the patients with PC in our study were between 60 and 69 years old. Moreover, our findings showed total negativity for MMP-26 in the group of atrophic cases, which might be useful for therapeutic definition as a predictive marker in such patients who also have high PSA. Besides, MMP-26 can be measured in serum, as described

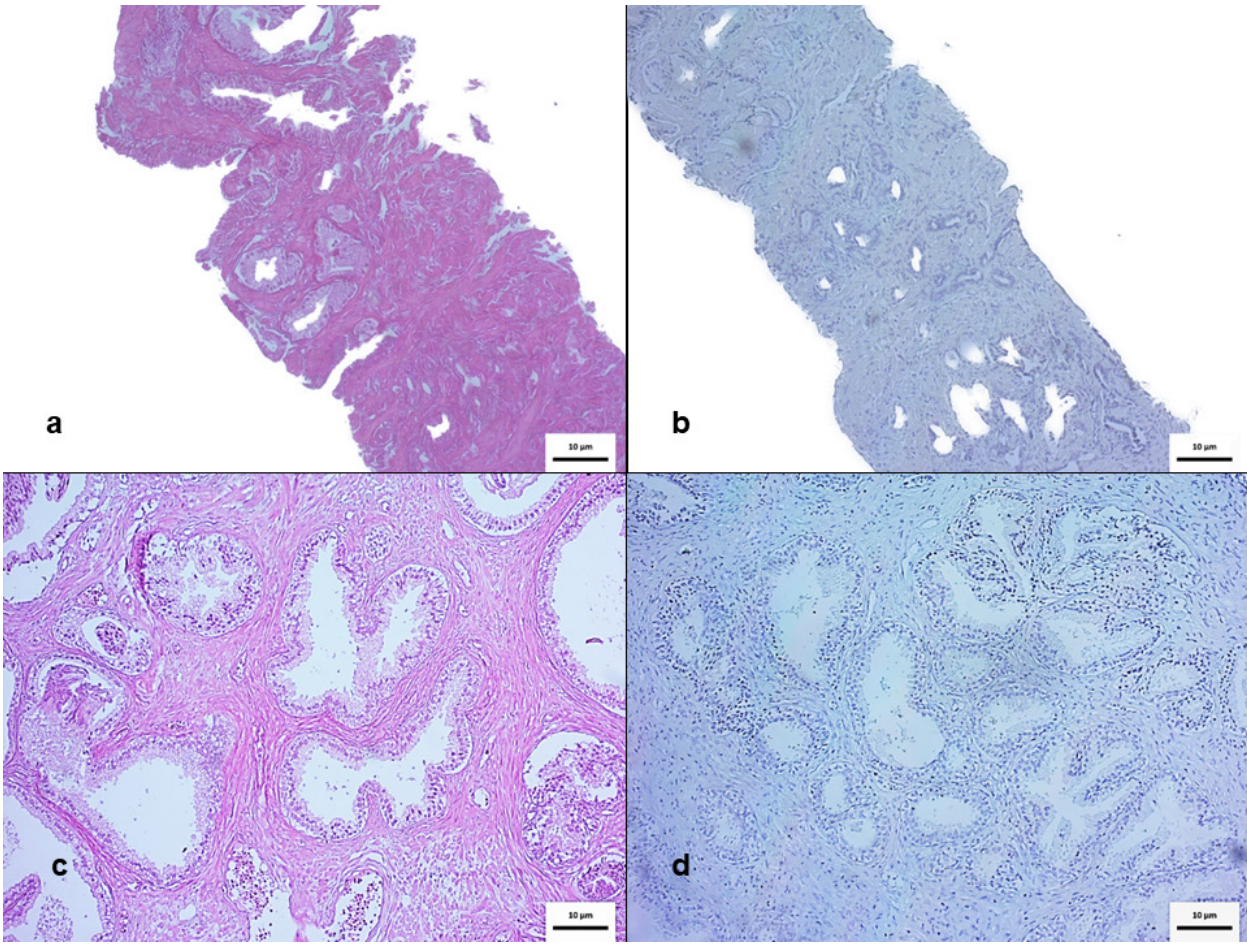


Figure 1. Photomicrographs of the prostate (10µM). Histopathological analysis (HE) on the left and immunohistochemistry (MMP-26) on the right. Absence of reactivity in the atrophy (a and b) and hyperplasia (c and d) groups. Scale bar 10 um.

by Cheng et al. (2017) in their study. Thus, it would be possible to concomitantly evaluate PSA and MMP-26 in the same blood sample and estimate the outcome of patients at risk in a given age group.

Ethnicity can also be a risk factor, blacks are more susceptible, according to a study by Noone et al. (2017), which contradicts our results: 44% of the samples were obtained from mixed races and 19% from blacks (with 10% presenting CP). It is known that smoking promotes an increase in mortality among patients with CP (Wilson et al. 2016). However, this association was also not found and can be explained by the case selection

being based on histopathological alteration and not spontaneous demand.

Unlike most MMPs, MMP-26 is expressed in the intracellular region (Khamis et al. 2013). The cytoplasmic immunoreactivity of MMP-26 was evidenced by Guo et al. (2018) in glioma cells and by Hu et al. (2014) in colorectal carcinoma. We observed both a cytoplasmic and nuclear pattern in malignant PC. This differentiated location enables new roles for this enzyme. Although the expression of MMP-26 is elevated in several types of cancer such as liver, lung and breast cancer (Yu et al. 2015, Zhao et al. 2015, Lee et al. 2011), some studies have also revealed protective functions in the regulation

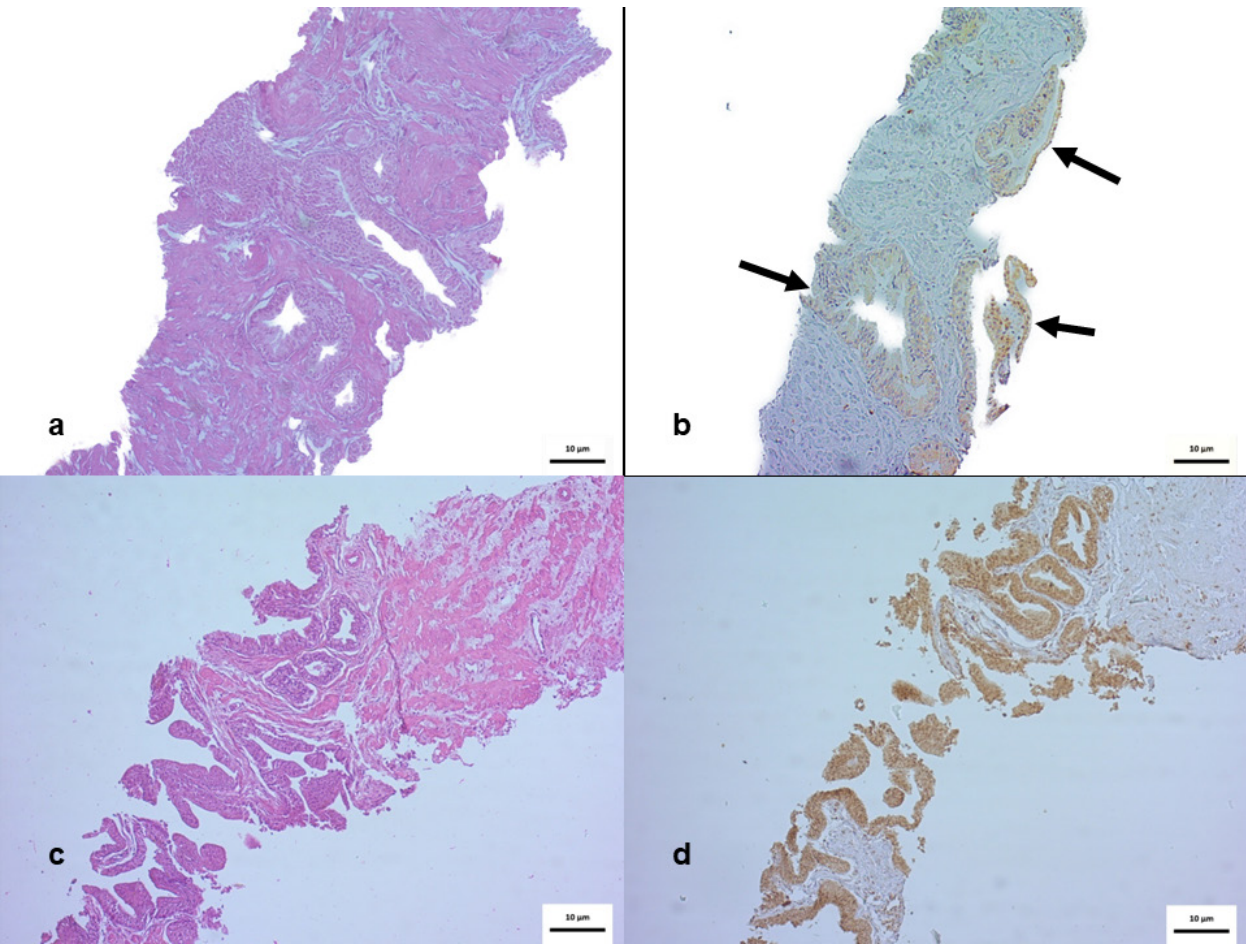


Figure 2. Photomicrographs of the prostate (10µM). Histopathological analysis (HE) on the left and immunohistochemistry (MMP-26) on the right. Weak reactivity in most cases of intraepithelial neoplasia (a and b) and moderate and intense immunoreactivity in the adenocarcinoma group (c and d). Scale bar 10 µm.

of inflammation and apoptosis (Khamis et al. 2013, 2016, Savinov et al. 2006).

Khamis et al. (2013) suggested an anti-inflammatory role for MMP-26. Cells transfected with MMP-26 cDNA showed low regulation of inflammatory genes, whereas cells with the silenced gene had reduced IL-10 receptor (IL10R), suggesting that MMP-26 deficiency may promote inflammation by inhibiting the IL10R pathway. Subsequently, Khamis et al. (2016) provided evidence for a protective role in the prostate. It was observed that prostate tumor cells expressing MMP-26 underwent apoptosis via Bax and that MMP-26 overload would have a pro-apoptotic function, reducing the degree

of invasion and disease progression. It was also observed by Savinov et al. (2006) that the elevation of MMP-26 resulted in a favorable prognosis and increased survival of patients with breast carcinoma *in situ*.

Given the versatile profile of MMP-26, there is still much to be investigated. However, several studies have clearly demonstrated its potential as a tumor marker, especially for prostatic carcinoma. In this study, we showed that the MMP-26 IHC can be potentially useful to differentiate benign and malignant cases of the prostate, and may assist in the development of new strategies for the diagnosis, prognosis, and treatment of prostate cancer.

Table IV. Assessment of IHC intensity for MMP26.

			Positive								
Group	Negative		Weak		Moderate		Strong		Group Total		p-Value
	n	%	n	%	N	%	n	%	n	%	
Atrophy	25	100	-	-	-	-	-	-	25	100	p ⁽¹⁾ < 0,001*
NIP	3	12	22	88	-	-	-	-	25	100	
HPB	48	96	2	4	-	-	-	-	50	100	
ACP	4	8	10	20	31	62	5	10	50	100	
TOTAL	80	53.3	34	22.7	31	20.7	5	3.3	150	100	

(*) Significant difference at 0.05. (1) Fisher's exact test.

Table V. Evaluation of PSA and clinical exams according to IHC.

Variable	Immunohistochemistry						p-Value p	Intensity (IHC)						p-Value
	Total		Negative		Positive			Weak		Moderate		Strong		
	n	%	n	%	n	%		n	%	n	%	n	%	
Total PSA							p ⁽¹⁾ = 0.002*							p ⁽²⁾ = 0.031*
< 4	37	27.2	27	38.6	10	15.2		5	15.6	5	17.2	-	-	
4 to 10	72	52.9	35	50	37	56.1		18	56.3	16	55.2	3	60	
> 10	27	19.9	8	11.4	19	28.8		9	28.1	8	27.6	2	40	
TOTAL	136	100	70	100	66	100		32	100	29	100	5	100	
Clinical examination							p ⁽¹⁾ = 0,945							p ⁽²⁾ = 0,905
Present nodule	36	33,6	18	34	18	33.3		7	30.4	9	33.3	2	50	
without nodule	71	66.4	35	66	36	66.7		16	69.6	18	66.7	2	50	
TOTAL	107	100	53	100	54	100		23	100	27	100	4	100	

(*) Significant difference at the level of 5.0%. (1) Using Pearson's Chi-square test. (2) Through Fisher's exact test.

Our results show that the immunohistochemical expression of MMP-26 is significantly higher in prostate adenocarcinoma samples compared to benign lesions such as atrophy and hyperplasia. This observation is consistent with previous studies suggesting that MMP-26 may serve as a useful biomarker for distinguishing between benign and malignant tissue in the prostate.

Furthermore, we observed a significant association between the intensity of MMP-26 expression and total PSA level, confirming the potential utility of MMP-26 in the prognostic assessment of prostate cancer. The lack of reactivity in atrophy and weak reactivity in

prostate intraepithelial neoplasia (PIN) reinforce the specificity of MMP-26 for malignant lesions.

It is important to highlight that coordinated expression of MMP-26 and TIMP-4 was observed in preinvasive prostate tumors. Lee et al. (2006) showed that maximal expression of MMP-26 and TIMP-4 occurs in high-grade prostatic intraepithelial neoplasia (HGPIN), with a significant decrease as the tissue progresses to invasive cancer. This coordination suggests that both markers may play a crucial role in the initial malignant transformation and progression of prostate cancer (Lee et al. 2006). Inclusion of this information in our study highlights the importance of considering the expression

of TIMP-4 along with MMP-26 for a better understanding of the molecular mechanisms involved in prostate carcinogenesis.

Our results, together with the existing literature, suggest that MMP-26 may be a valuable biomarker for the diagnosis and prognosis of prostate cancer. The coordinated expression of MMP-26 and TIMP-4 could provide additional insights into tumor progression and potentially guide new therapeutic strategies.

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All authors contributed to the conception and design of the study. The collection and processing of the material, as well as the immunohistochemical analyzes, were performed by Romildo Luciano da Silva, Francisco Luís Almeida Paes, Sandra Maria Souza da Silva and Fabiano Santos. The analysis of the data and results obtained was carried out by Jacinto Costa da Silva Neto. The revision and editing of the manuscript were carried out by Jacinto Costa da Silva Neto and Eduarda Santos de Santana. The financing was acquired by Jacinto Costa da Silva Neto. The research was supervised by Jacinto Costa da Silva Neto. All authors read and approved the final manuscript.

