The Association between Matrix Metalloproteinase-9 (MMP-9) Immunohistochemical Expression and Gleason Grading System International Society of Urological Pathology (ISUP) in Prostate Adenocarcinoma

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ABSTRACT

Background
Prostate cancer is the fourth ranked malignancy and the eighth leading mortality worldwide. The Gleason grading system is used to evaluate the tumor grade. The highest the score, theworst and the most aggressive the nature of tumor, which associated with invasive behaviour.In prostate carcinoma, Matrix Metalloproteinase-9 (MMP-9) is involved in all stages of cancercell progression include proliferation, angiogenesis, apoptosis, epithelial-mesenchymal transition (EMT) and metastasis. MMP-9 degrade the surrounding tumor matrix and neural tissue during perineural invasion in prostate carcinoma which is a prerequisite for invasion andmetastasis. The aim of this research is to evaluate the correlation of MMP-9 immunohistochemical expression with the Gleason Grading System International Society of Urological Pathology (ISUP) of prostate adenocarcinoma.

Methods
Cross sectional analytic study using 32 samples diagnosed as prostate adenocarcinoma at H.Adam Malik General Hospital Medan were performed. Staining was performed using a polyclonal antibody rabbit MMP-9 immunohistochemistry (Bioenzy) which would appearpositive in the cytoplasm and in stroma of the tumor cell at a dilution of 1:100 (overnight). MMP-9 expression was assessed semi quantitatively based on intensity and tumor cell distribution with four-tier expression categories. Data analysis was tested with the Kruskal- Wallis test.

Results
Most cases (53.1%) were strongly positive with MMP-9 and MMP-9 immunohistochemical expression has a significant relationship with Gleason Grading ISUP System of prostate adenocarcinoma (p:0.0007).

Conclusion
There was a significant association between MMP-9 immunohistochemical expression and the Gleason Grading ISUP System of prostate adenocarcinoma.

Keyword: Prostate adenocarcinoma, ISUP, Gleason grading, matrix metalloproteinase-9

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INTRODUCTION

Prostate adenocarcinoma is the most common histological type of prostate cancer (95% of all prostate malignancy) according to data from the Global Burden of Cancer (GLOBOCAN). The incidence of prostate cancer ranks fourth in the world with 414,259 new cases and the eighth leading cause of mortality (375,304 cases).[1,2] Geographically, there are wide differences in incidence particularly high Human Development Index (HDI) countries, include European countries (33.5%) and North America (16.9%). This may be due to differences in the use of Prostate Serum Antigen (PSA) serum for prostate cancer screening among these countries, in addition to the role of environmental and genetic factors.[3-5]

In Indonesia (2020), the incidence of prostate cancer is the fifth most common cancer in men with 13,563 (7.4%) new cases and 4,863 (2.1%) deaths. Provinces with the highest prostate cancer prevalence were Yogyakarta, Bali, North Sulawesi, and South Sulawesi at 0.5%.[2] The increasing incidence of prostate cancer is associated with several risk factors such as: age, genetic factors, family history, ethnicity, smoking, obesity, diet, and DNA repair genesmutations. Levels of sex hormones such as dihydrotestosterone (DHT) (which will bind to androgen receptors) are also said to take a role in the growth and development of prostate adenocarcinoma. The prognosis of patients with prostate cancer varies greatly depending onthe grade and the stage of tumor at diagnosis. About 80% of men are diagnosed at an early stage with tumors confined to the prostate, 15% with locoregional metastases, and 5% with distant metastases. Patients who are diagnosed at an advanced stage and usually have distant metastases, have a poor prognosis with a 5 years survival rate is only 30%.[5-7]

The interactions between cancer cells and the tumor microenvironment had been widely studied and the previous studies had linked these interactions to the process of tumor invasion and metastasis.[8] The invasion and metastatic ability of a cancer plays an important role in the progressivity and aggressiveness of cancer cells and is a major cause of cancer morbidity and mortality.[9] Cancer cells degrade various components of the extracellular matrixto invade the stroma around the tumor and to migrate towards other tissues, such as nerve tissue (perineural invasion). This process is regulated by proteolytic enzymes, including MatrixMetalloproteinases (MMPs). MMPs takes an important role in tissue growth, differentiation, and remodelling, as well as tumorigenesis, invasion, angiogenesis, anti-apoptosis, and cell migration associated with tumor progression.[10,11] MMPs are highly expressed in malignant tumors and a significant correlation between increased MMP expression and poor prognosis is revealed.[12]

Several studies have shown an association between increased MMP expression and poor outcome in various solid tumors. Among all of the MMP family's members, Matrix Metalloproteinase-9 (MMP-9) has shown an influence on the prognosis and survival of patients with prostate cancer.[13] In prostate adenocarcinoma, this aggressiveness is determined by the grade of the tumor as assessed by the Gleason grading system. The higher the Gleason score, the worse and more aggressive the nature of the tumor.[14] The Gleason grading systemis used worldwide and has been modified over the past 50 years, most recently at the International Society of Urological Pathology (ISUP) conference in 2019.[3] MMP-9 is involved in all stages of cancer cell progressivity from proliferation, angiogenesis, apoptosis, epithelial- mesenchymal transition (EMT) and metastasis of prostate adenocarcinoma where several studies have shown that MMP-9 expression increased in prostate carcinoma. MMP-9 takes an important role in degrading the matrix surrounding tumor and nerve tissue during perineuralinvasion.[11,13]

In prostate carcinoma, MMP-9 is a novel biomarker that reflects the invasion and metastatic potential of prostate carcinoma. The more MMP-9 is expressed, the worse the prognosis.[11,13] Standard biomarkers that significantly predict clinical and biochemical recurrence of prostate cancer are preoperative serum PSA, histopathologic grading based on Gleason score, positive operative margin (with and without extraprostatic extension), and capsular incision in addition to the following prognosis factors, include presence or absence of perineural invasion, angiolymphatic, invasion to seminal vesicles and extraprostatic tissue.[14,15] A study conducted by Cardillo et al found that high MMP-9 expression was closelyrelated to high Gleason score.[16] Ozden et al in their study

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also reported that MMP-9 expressionwas more expressed in higher Gleason score.[11] Mahastuti et al also found that MMP-9 was more expressed at higher grade compared to low grade tumor.[17] The other hand, Oguic et alfound there was no significant difference in MMP-9 expression levels between high grade andlow grade prostate adenocarcinoma. Significant differences were found only in tumor tissue which containing tumor cells at the resection margin.[14]

The high incidence and mortality of prostate adenocarcinoma especially in patients diagnosed at an advanced stage, some previous research results that are still controversial are the basis for the author to conduct this research. The aim of the study is to evaluate the association of MMP-9 immunohistochemical expression with prostate adenocarcinoma grading, in which MMP-9 can be considered as one of the additional prognosis factors and the development of target therapy particularly in cases of prostate adenocarcinoma.

METHODS

The design of this research was an analytic study with a cross sectional approach. The study was conducted at the Anatomic Pathology Laboratory of H. Adam Malik Hospital Medan using paraffin blocks and slides from TURP and core biopsy samples that had been histologically diagnosed as prostate adeno-carcinoma. Sample calculation was carried out, obtained a total 32 samples, including inclusion criteria paraffin blocks and slides from TURPand core biopsy procedures that were histologically diagnosed as prostate adenocarcinoma using hematoxylin-eosin (HE) staining with Gleason score ≥6, where exclusion criteria were missing or unrepresentative paraffin blocks/slides which could not be processed, cut and re- staining. Gleason score ISUP system was determined by summing 2 most prevalent Gleasongrade, which obtained from assessment of glandular architectures microscopically. Gleason grade group is categorized into 5 categories, that is group grade I-V.

Immunohistochemical staining of MMP-9 was performed by using rabbit polyclonal antibody (BZ-0898450; BioEnzy) that was diluted at 1:100 (4^0C, overnight). MMP-9 expression was identified by the presence of brownish staining in the cytoplasm of tumor cells and stroma around the tumor cells. Immunoreactivity was semi-quantitatively evaluatedby integrating the percentage of tumor cells stained and the intensity of staining. The intensityof staining was scored as follows: score 0 (not stained/negative), score 1 (weak), score 2 (moderate), score 3 (strong).[17] The percentage of stained tumor cells was categorized into 4 grades: score 0 (0%), score +1 (<25%), score +2 (25-75%), score +3 (>75%). The multiplication of the intensity and the percentage of stained tumor cells (nominal scale) was considered as follows: 0=negative (score 0), 1=weakly positive (score 1-2), 2=moderately positive (score 3-4), and 3=strongly positive (score 5-9). Immunohistochemical staining was evaluated and scored by two independent pathologists and the researcher. The correlation of MMP-9 expression level and Gleason grade ISUP was determined by Kruskal-Wallis test analysis. All p-value <0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Thirty-two samples of prostate adenocarcinoma were obtained in this research. Table 1 shows the distribution of sample characteristics based on age, Gleason Grading System, and MMP-9 immunohistochemical expression of prostate adenocarcinoma.

Table 1. Characteristics of 32 patients with prostate adenocarcinoma.

Characteristics	N	%
Age		
<60 years old	2	6.2
60-70 years old	14	43.8
>70 years old	16	50.0
Gleason grading ISUP		
Grade group I: Gleason score ≤6	4	12.5
Grade group II: Gleason score 3+4=7	2	6.2
Grade group III: Gleason score 4+3=7	3	9.4
Grade group IV: Gleason score 8	7	21.9
Grade group V: Gleason score 9-10	16	50.0
MMP-9 immunohistochemical expression		
0=negative (score 0)	0	0
1=weakly positive (score 1-2)	5	15.6
2=moderately positive (score 3-4)	9	28.12
3=strongly positive (score 5-9)	18	56.25

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According to table 1, the most of the patients were in the group of age over 70 years old (50%), with the oldest was 93 years old and the youngest was 57 years old. Based on Gleason grading system assessment (Grade group I-V), most samples (16 samples) were grade group V tumors (50.0%), followed with 7 samples (21.9%) were grade group IV, 4 samples (12.5%) were grade group I, 3 samples (9.4%) were grade group III, and 2 samples (6.2%) were grade group II. All samples expressed MMP-9 immunohistochemical expression,in which strongly positive expression were noted in 18 samples (56.25%), followed with 9 samples showed moderately positive, 5 samples of weakly positive expression.

Table 2. The correlation between Matrix Metalloproteinase-9 expression and Gleason Grading SystemInternational Society of Urological Pathology (ISUP) of prostate adenocarcinoma.

Histological Grade	MMP-9 expression								p-value
	Negative		Mild		Moderate		Severe		
	n	%	n	%	n	%	n	%	
Grade group I	0	0	4	100.0	0	0	0	0	
Grade group II	0	0	0	0	2	100.0	0	0	
Grade group III	0	0	1	33.3	1	33.3	1	33.3	0.001
Grade group IV	0	0	0	0	1	14.3	6	85.7	
Grade group V	0	0	0	0	5	33.3	11	68.7	

*Kruskal-Wallis test

Correlation test analyses using Kruskal-Wallis test was summarized in table 2 which displayed that MMP-9 expression levels significantly correlated with Gleason grading system ISUP of prostate adenocarcinoma ($p<0.05$). Representative histological images of prostate adenocarcinoma and MMP-9 expression levels are shown in Figure 1 and 2 respectively.

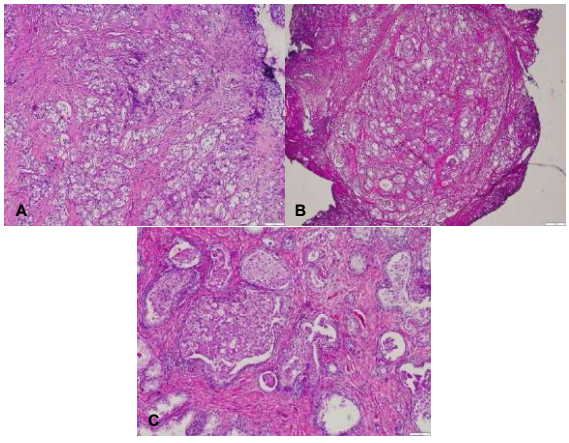

Figure 1. Histological pattern of prostatic adenocarcinoma. A. Pattern 3 (HE, 100 times). B. Pattern 4(HE,100 times). C. Pattern 5 (HE, 100 times).

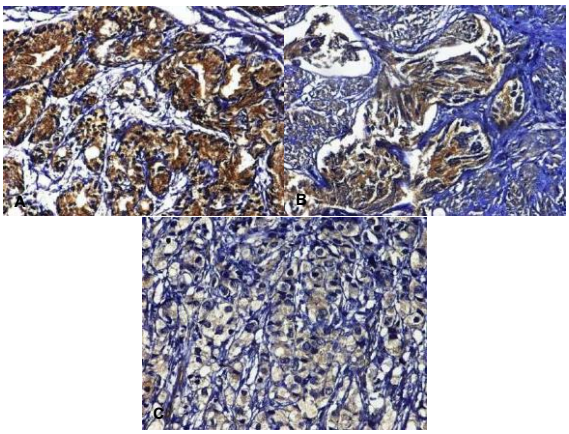

Figure 2. MMP-9 immunohistochemical expressions. A. Strongly positive expression. B. Moderatelypositive expression. C. Weakly positive expression.

DISCUSSION

In our study, we found that prostate adenocarcinoma mostly occurred at the age of over 70 years old (50%). These results are in line with previous research conducted by Siregaret al (2020), which found that most prostate adenocarcinoma patients were aged >71 years old (56.3%).[18] Research by Mahastuti et al (2017) also found that most prostate adenocarcinoma patients were aged >50 years old. In 2012, research conducted by Laksmi et al revealed that most prostate adenocarcinoma patients were at the age of 66-84 years old,that was 39 cases (71.4%).[19] This is in accordance with the literature which states that prostate

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adenocarcinoma patients will increase according to age, the accumulation of somatic mutations during the aging process facilitates malignant transformation in old age, only a few prostate adenocarcinoma patients under 40 years old and 80% are found at the age of over 80 years old, during the aging process there is an accumulation of genetic and epigenetic changes, accumulation of free radicals due to oxidative stress and progressive damage to DNA repair mechanisms, cell cycle control and stem cell renewal involved in carcino-genesis.[17,18] Predominantly old-age prostate adenocarcinoma patients is due to prolonged exposure to androgen hormones, where androgens have an important role in the development and growth of prostate adenocarcinoma.[17] The youngest patient found in this study was 57 years old and the oldest was 93 years old. This is in accordance with WHO which states that there are only 1% of prostate adenocarcinoma patients at the age of <50 years old. However, several cases of prostate adenocarcinoma in children under 10 years old and between 10 and 21 years old were noted. The cause of prostate adenocarcinoma at a younger age was strongly related to lifestyle and diet. There is evidence that glandular epithelial cell injury due to carcinogens, estrogens or oxidants are the precipitating factors forchronic inflammation and a stage of cancer cell development.[3]

Most of patients (16 samples; 50.0%) in this study showed Gleason score 9-10 basedon the Gleason grading system ISUP. In accordance with the previous research conducted bySiregar et al in 2020 which also found the most patients (14 samples out of 32; 43.8%) had Gleason score 9-10.[19] Research by Mahastuti et al (2017) found that most prostate adenocarcinoma patients were high grade with a percentage of 66.67%.[17] On the other side, research by Shah et al obtained in 2006-2010 there were 61% samples with Gleason score 7-10 and in the year 2011-2015, 1059 of 1435 samples (74%) were Gleason score 7-10.[20] In contrast to the results of research reported by Baspinar et al (2016) and Oguic et al (2014) also found the most cases were Gleason score ≤6 (41.3% and 65.4% respectively).[10,14] Research by Ozden et al (2013) found the most cases were Gleason score 7 (47.5%).[11] Trudelet al in 2010 found the most cases were Gleason score ≤6 (60.0%).[16] Based on the WHO Classification of Urinary and Male Genital Tumors (5th ed.), the Gleason grading system is divided into 5 scores ranging from score 1 (most differentiated) to score 5 (least differentiated) on the architectural pattern of prostate cancer. the International Society of Urological Pathology (ISUP) Gleason Grading System assessment of prostate adenocarcinoma states that the Gleason score is an independent predictor of recurrence, metastasis, and prostate cancer-specific mortality.[3] The Gleason grading system is used to help plan the most appropriate therapy and action for prostate adenocarcinoma patients, such as surgery, radiation therapy or hormone therapy.[21]

Based on MMP-9 immunohistochemical expression, most of samples showed strongly positive expressions as many as 18 samples (56.25%), in line with previous research by Moraes et al (2021) where most samples were MMP-9 overexpressed (58.5%) compared to MMP-9 under-expressed (41.5%) samples. In contrast to Baspinar et al in 2016 found the most MMP-9 expression at +2 positive (moderate) in 53 samples.[10] Study by Trudel et al (2010) found MMP-9 expression at +1 expression in 76 samples (41.1%).[16] Strong expressionof MMP-9 in prostate adenocarcinoma cases that have been studied were found mostly in grade group V with Gleason score 9-10. This in line with this study where most samples weregrade group V with strong MMP9 expression. Another possibility is that growth factors and cytokines expressed by tumor cells, stroma, and inflammatory cells in the tumor micro-environment may lead to increased expression of MMP-9 through autocrine and paracrine pathways.[17]

Kruskal-Wallis test revealed that there was a significant association between MMP-9 expression and Gleason Grading System ISUP in prostate adenocarcinoma with p=0.001 (p<0.05). MMP-9 expression was strongly positive in grade group V (Gleason score 10). This study is in line with previous research conducted by Mahastuti et al in 2017 showing that the high-grade prostate adenocarcinoma group (Gleason score ≥7), the higher MMP-9 expression compared to low grade prostate adenocarcinoma.

The study is in accordance with the theorywhere Gleason score ≥7 which indicates

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an infiltrative tumor pattern that causes many tumor cells to interact with the tumor micro-environment which may cause strong expression of MMP-9.[17] Research by Trudel et al in 2010 reported that strong expression of MMP-9 in cancer cellsis a sign of cancer aggressiveness, and also poor prognosis.[12,16] Research by Cardillo et al in 2006 reported that MMP-9 expression of high grade prostate adeno-carcinoma (Gleason score ≥7) had higher MMP-9 expression than low grade prostate adenocarcinoma. The presence ofstrong MMP-9 expression indicates changes in the tumor microenvironment that can lead to tumor invasion and metastasis.[23]

In contrast to previous research conducted by Babichenko et al (2014) reported that prostate adenocarcinoma grade group II had strong MMP-9 expression. This may occur due to the invasive nature of tumor cells, which leads to the degradation of type IV collagen in thebasement membrane and stromal tissue of the prostate, caused by dysregulation between MMP-9 and TIMP-1-a TIMP-1 protein which will inhibit the MMP-9 enzyme.[24] Research by Oguic et al reported a significant relationship was found in biochemical recurrence and MMP-9 expression in the group of patients with negative resection margins. Multivariate analysis showed MMP-9 expression to be a significant predictor of biochemical recurrence. Together with MMP-2, MMP-9 expression may provide useful information to predict prostate tumor behavior after prostatectomy in both positive and negative resection margin. MMP-9 expression in prostate adenocarcinoma was stronger in Gleason score ≥7 compared with Gleason score <7. Significant differences were only found in tumor tissue with positive tumor resection margin. This may be related to the balance of the amount of enzyme and its inhibitor (TIMP-1).[14] Research by Ozden et al in 2013 reported that MMP-1 expression was not correlated with Gleason score of prostate adenocarcinomas.[11]

In addition, more extensive studies on substrate identification have shown that MMP9 also participates in the release or activation of a wide variety of bioactive molecules, such as growth factors, chemokines, cytokines and matrikines, which are responsible for cell migration,differentiation and survival as well as immune response, angiogenesis, or tumor microenvironment formation. Increased MMP-9 expression is frequently observed in various cancers, and in many cases, positively correlates with tumor stage and poor clinical outcome. This makes MMP-9 become an attractive target for cancer therapy. However, efforts to develop safe and effective drugs that selectively target MMP-9 are difficult, due to the highly conserved active side among MMP family members and its dose-limiting toxicity and side effects. Therefore, recent studies have led to the development of a functional blocking antibody that selectively inactivates MMP-9, the specific antibody andecaliximab which is currently in clinical trials in participants with advanced solid tumors. On the other hand, although considered a mediator of pro-tumorigenic effects, MMP-9 was also found to promoteregression of certain tumors. Future studies should focus more on a deeper understanding of the mechanisms by which MMP-9 contributes to cancer growth, progression, and spread which will promote the development of next-generation therapies for MMP-9-targeted therapies for cancer.[25]

CONCLUSION

The most common age of prostate adenocarcinoma patients in this study was >70 years old (50%). The most common grade of prostate adenocarcinoma based on Gleason grading System International Society of Urological Pathology (ISUP) was grade group V: Gleason score 9-10. Immunohistochemical expression of Matrix Metalloproteinase-9 in prostate adenocarcinoma predominantly was strongly positive expression (56.25%). In addition, the results of statistical analysis revealed the significant correlation between MMP-9 immunohistochemical expression and Gleason grading system ISUP of prostate adenocarcinoma (p=0.001).

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