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HIGH MATRIX METALLOPROTEINASE 9 EXPRESSION AS A RISK FACTOR OF LYMPHOVASCULAR INVASION IN CERVICAL CARCINOMA

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Abstract

Background: Cervical carcinoma is an epithelial cancer with the highest mortality among female genital malignancies. Its poor prognosis is largely related to metastasis, which begins early through lymphovascular space invasion (LVSI). LVSI occurs when cancer cells invade surrounding tissue via proteolytic enzymes, but early prediction remains difficult. Although several molecular markers have been studied, none is definitive, and the role of matrix metalloproteinase-9 (MMP-9) in LVSI remains controversial.
Objective: This study will prove MMP-9 as a risk factor for LVSI in cervical carcinoma
Methods: This case–control study analyzed 40 archived paraffin-embedded tissue blocks from cervical carcinoma patients at BaliMed Denpasar Hospital. Immunohistochemical staining was performed to assess MMP-9 expression, while hematoxylin and eosin (H&E) staining was used to evaluate lymphovascular space invasion (LVSI). Statistical analysis was conducted using the chi-square test in SPSS version 25.
Results: The study showed that 85,7% of cervical carcinomas with LVSI have high MMP-9 expression, with a significant result compared to cervical cancer without LVSI (p=0.001, OR= 13.5).
Conclusions: The MMP-9 expression was significantly associated with the risk of LVSI in cervical carcinoma

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INTRODUCTION

Cervical carcinoma is an epithelial cancer of the cervix that causes the highest mortality among all female genital cancers in developing countries, including Indonesia (1,2). The progression of cervical carcinoma is relatively fast, and it is even very susceptible to causing distant metastasis. One of the triggering factors for distant metastasis in cervical carcinoma is lymphovascular invasion (LVSI). Until now, predicting the possibility of metastasis in cervical carcinoma has been an obstacle. The finding of metastasis can occur several months or years after the histopathological diagnosis of cervical carcinoma is confirmed. In reporting the histopathological results of cervical carcinoma, the diagnosis will be accompanied by the stage, grade of cancer, and findings of LVSI. LVSI is the initial process that triggers metastasis, which is confirmed histopathologically if there is a picture of cancer cell emboli in the lumen of blood vessels lined with endothelial cells (1,3). However, until now, it has been difficult to predict the possibility of intravascular invasion earlier.

Clinically, LVSI is one of the three Sedlis criteria in determining the need for adjuvant therapy, such as chemoradiation, after radical hysterectomy. The finding of LVSI is one of the critical factors that affect the prognosis and management of cervical carcinoma. LVSI is the process by which cancer cells infiltrate the lymphatic and blood vessels, spreading cancer cells to other body parts (1,4,5). This process is very complex and involves various molecules and different signaling pathways. One group of enzymes that plays a vital role in invasion and metastasis is matrix metalloproteinases (MMPs), especially MMP-9. MMP-9, or gelatinase B, is a proteolytic enzyme that can degrade extracellular matrix (ECM) components, such as type IV collagen and gelatin (2,6,7,8). Degradation of the ECM by MMP-9 facilitates the movement of cancer cells through the surrounding tissue and into the blood and lymphatic vessels (9). In addition, MMP-9 is also involved in modulating the tumor microenvironment, which can support the growth and spread of cancer cells. Previous studies have shown that MMP-9 expression is increased in various types of cancer, including cervical carcinoma, and that the level of MMP-9 expression correlates with tumor aggressiveness and poor prognosis (9,10,11,12,13). Other studies have also found a positive correlation between MMP-9 and lymph node metastasis (14,15,16,17,18). However, the specific mechanism by which MMP-9 affects LVSI in cervical carcinoma is still not fully understood.

MATERIALS AND METHODS

This study employed an analytical case–control design at BaliMed Denpasar Hospital, involving 40 cervical carcinoma patients. Participants were selected through simple random sampling based on predefined inclusion and exclusion criteria. The specimens consisted of archived paraffin blocks from histopathologically confirmed cervical carcinoma cases stored at BaliMed Denpasar Hospital during 2022–2023. Paraffin blocks were included if they contained confirmed cervical carcinoma tissue, and excluded if they were damaged or lacked sufficient tumor material.

Patient age and tumor size were obtained from medical records. MMP-9 expression was assessed by immunohistochemistry (IHC) using a monoclonal rabbit anti-human MMP-9 antibody (Cell Marque, USA), while tumor budding grade was evaluated using hematoxylin and eosin (H&E) staining. Age was categorized as >50 years or ≤50 years, and tumor size as <2 cm or ≥2 cm. For IHC assessment, MMP-9–positive cells appeared as brown

cytoplasmic staining in malignant epithelial cells. MMP-9 expression was classified as high when >10% of tumor cells showed cytoplasmic staining and low when <10% were stained. An anatomical pathologist evaluated the slides under 400× magnification across five different fields of view.

All variables were tabulated and analyzed. Univariate analysis described subject characteristics using frequency distributions. Bivariate analysis was performed using the Chi-square test in IBM SPSS version 25 to examine whether high MMP-9 expression represents a risk factor for lymphovascular invasion in cervical carcinoma.

RESULTS AND DISCUSSION

This study found that the most significant sample was in the age group <50 years, which was 55%, with the majority in that age group being in the 4th decade. The results of this study indicate consistency with similar research at the Prof. Dr. I.G.N.G. Ngoerah Central General Hospital in 2017, which stated that the highest incidence of cervical cancer was at the age of 41-50 years (20).

Furthermore, a previous study conducted at Dr. Kariadi General Hospital, Semarang, reported the highest incidence of cervical cancer among women aged 41–50 years (21). In the present study, the distribution of tumor sizes within the sample was relatively balanced, with 52.5% of cases in the cervical carcinoma group having tumors ≥2 cm and 47.5% with tumors <2 cm. To minimize potential bias from tumor size on the study outcomes, tumor size categories were standardized across both groups.

Previous research by Huang et al. (2016) demonstrated a significant association between tumor size and both the degree of tumor budding and invasiveness ($p = 0.002$). Similarly, Park et al. (2020) reported that tumor size holds prognostic significance in cervical carcinoma, with larger tumors being more likely to metastasize distantly via the parametrium or vascular invasion, resulting in poorer prognosis ($p = 0.0129$). Consequently, tumor size was considered a critical confounding factor that required control in the present study.

As in Table 1, this study found that MMP-9 expression was closely related to LVSI in cervical carcinoma with a significance value of $p = 0.001$ ($p < 0.05$; OR 13.5). The result also shows that high MMP-9 expression increases the LVSI risk by 13.5 times in cervical carcinoma. The MMP-9 expression can be seen in Figure 1, which shows that more than 10% MMP-9 is stained in the cytoplasm of cervical carcinoma with positive LVSI (B), in contrast to cervical carcinoma with negative LVSI, which shows negative staining of MMP-9 IHC. Previous studies on thyroid carcinoma found that MMP-9 was related to extra-compartment invasion and metastasis to the lymph node (21,22,23).

MMP-9 is a proteolytic enzyme that plays a role in the degradation of extracellular matrix components, which allows cancer cells to invade surrounding tissues and spread to blood vessels and lymphatics. Based on various research results in the field of cancer, increased expression of MMP-9 is often found in more aggressive tumors and may indicate the ability of the tumor to metastasize. MMP-9 can break down collagen and other extracellular matrix components, which support cancer cells in moving and adapting to their new microenvironment. The mechanism of MMP-9 in increasing the ability of tumor invasion is (16,17,18,19,24,25).

1. Extracellular Matrix Degradation: MMP-9 helps break down the physical barrier between the tumor and blood or lymph vessels, facilitating the migration of cancer cells.

2. Interaction with Immune Cells: MMP-9 can attract immune cells to the tumor site, affecting the invasion process and response to therapy. Recruited immune cells, such as macrophages, can also produce factors that further promote MMP-9 expression, creating a positive feedback loop that enhances the invasion process (25,26).
3. Production and regulation of signaling molecules: MMP-9 releases growth factors such as VEGF and various cytokines that induce tumor growth and metastasis.
Therefore, it can be concluded that high MMP-9 expression in tumor tissue, including cervical carcinoma, is associated with an increased risk of LVSI and metastasis.

Table 1. MMP-9 expression between the 2 group samples (n=40)

Variables	Lymphovascular invasion (LVSI) group		p value	OR
	Positive N=20	Negative N=20		
MMP-9 Expression				
High	12(60.0%)	2(10.0%)	**0.001***	**13.5**
Low	8(40.0%)	18(90.0%)		

Remarks * explain the significant value of the statistical result

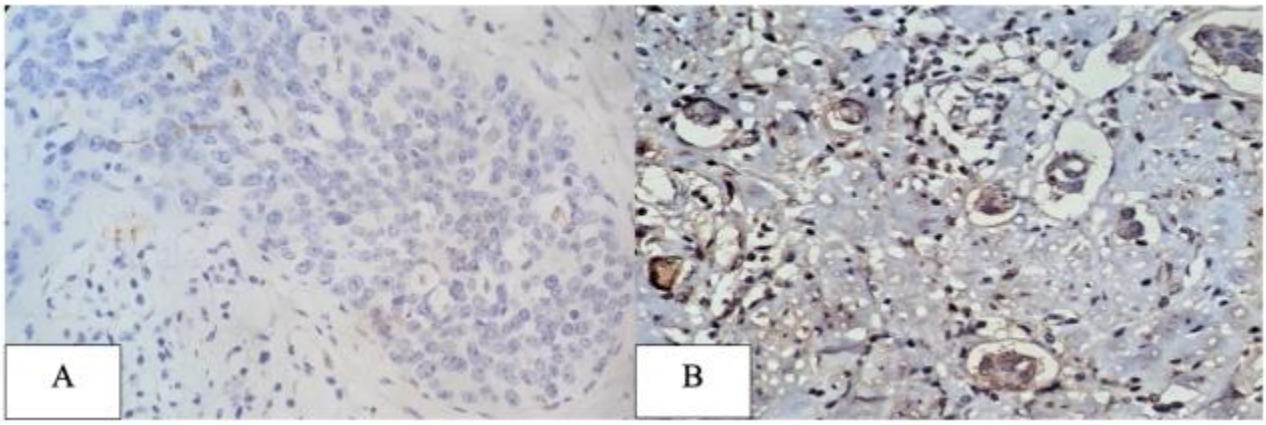

Figure 1. Comparison of MMP-9 expression between the 2 sample groups. A. Low MMP-9 expression in cervical carcinoma with negative LVSI, B. High MMP-9 expression in cervical carcinoma with positive LVSI

CLINICAL IMPLICATION

This study explores the role of MMP-9 in triggering LVSI in cervical carcinoma. MMP-9 testing could be implemented in pathology or oncology practice, such as it potential parameter as risk stratification for adjuvant therapy, or the assessment of necessity of aggressiveness treatment. A deeper understanding of this mechanism may provide new insights into the pathogenesis of cervical carcinoma and potentially identify new therapeutic targets to prevent or inhibit metastasis in patients with cervical carcinoma.

Thus, this study has the potential to contribute significantly to improving treatment strategies and prognosis for patients with cervical carcinoma.

LIMITATIONS

This study explores the role of MMP-9 in triggering LVSI in cervical carcinoma. MMP-9 testing could be implemented in pathology or oncology practice, such as it potential parameter as risk stratification for adjuvant therapy, or the assessment of necessity of aggressiveness treatment. A deeper understanding of this mechanism may provide new insights into the pathogenesis of cervical carcinoma and potentially identify new therapeutic targets to prevent or inhibit metastasis in patients with cervical carcinoma. Thus, this study has the potential to contribute significantly to improving treatment strategies and prognosis for patients with cervical carcinoma.

CONCLUSIONS

The expression of MMP-9 showed a significant correlation with an increased 13.5 times risk of lymphovascular invasion in cervical carcinoma. This suggests that MMP-9 may serve as a prognostic marker for the disease. Elevated MMP-9 expression appears to promote more aggressive tumor behavior, facilitating lymphovascular invasion and potentially driving further metastatic progression.

CONFLICT OF INTEREST

The authors affirm that this research was carried out without any commercial or financial involvement that could be interpreted as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ni Wayan Armerinayanti: Conceptualization, Methodology, Writing – Original Draft, Visualization, Supervision, Project Administration, Funding Acquisition, and Resource Provision.

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DECLARATION OF ARTIFICIAL INTELLIGENCE USE

The authors used ChatGPT (OpenAI, version GPT-3) to assist in improving the language and grammar of the manuscript. The authors reviewed and verified the content to ensure accuracy and integrity.

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