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The prognostic values of matrix metalloproteinases in ovarian cancer

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Abstract

Objective: To investigate the prognostic significance of 23 matrix metalloproteinase (*MMP*) genes in patients diagnosed with ovarian carcinoma.

Methods: The prognostic significance of 23 *MMP* genes in patients diagnosed with ovarian carcinoma was investigated using the Kaplan–Meier plotter (KM plotter), which uses the gene expression data and overall survival information of patients with ovarian cancer that were downloaded from the Gene Expression Omnibus, Cancer Biomedical Informatics Grid and The Cancer Genome Atlas cancer datasets. The correlation between mRNA levels of individual MMPs (MMP2, MMP9, MMP10, MMP12, MMP13 and MMP25) and clinicopathological features (histological subtype, pathological grade and clinical stage) were investigated. The MMP protein level profiles in normal ovarian tissues and ovarian cancer tissues were examined using the Human Protein Atlas database.

Results: The results showed that high mRNA levels of MMP2 and MMP13 were associated with a worse overall survival in patients with ovarian cancer, whereas high mRNA levels of MMP9, MMP10, MMP12 and MMP25 were associated with a better overall survival. The protein levels of MMP2, MMP9, MMP10 and MMP25 in ovarian cancer tissues were elevated compared with normal ovarian tissues.

Conclusions: This study demonstrated that MMPs can be a reliable prognostic biomarker for ovarian cancer.

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Introduction

Ovarian cancer, which accounts for approximately 22 240 newly-diagnosed cases and 14 070 cancer-related deaths annually in the United States, is the fifth most lethal malignancy among women.[1] Using a combination of maximal cytoreductive surgical debulking and platinum-based chemotherapy is the standard treatment for the advanced stages of ovarian cancer.[2] Despite the progress in conventional treatment approaches, which comprise of surgical techniques and contemporary systemic treatment regimes, the 5-year survival rate is only 47% for all stages combined.[3] Therefore, there is an urgent need to find reliable prognostic biomarkers and develop novel targeted therapies.

Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, play a crucial role in various physiological processes including tissue remodelling and organ development, the regulation of inflammatory processes and diseases such as cancer.[4,5] There are 23 members in the *MMP* gene family that are expressed in humans, many of which have been reported to be associated with multiple human cancers.[4] MMPs are frequently expressed in ovarian cancer and play an important role in the metastatic process.[6] MMPs mediate degradation of the basement membrane, which is a crucial step in epithelial transformation, ovarian tumorigenesis and intraperitoneal metastasis.[6]

A number of studies have investigated the association between *MMP* gene expression and survival in breast cancer patients, with overexpression of *MMP9* and *MMP2* indicating a higher risk of a poor prognosis.[7] However, the prognostic significance of the *MMP* gene family in ovarian cancer has not been completely elucidated. This study investigated the prognostic significance of 23 *MMP* genes in patients diagnosed with ovarian carcinoma using the Kaplan–Meier plotter (KM plotter). Then, MMP protein level profiles in normal ovarian tissues and ovarian cancer tissues were examined using the Human Protein Atlas database.

Patients and methods

KM plotter database and statistical analyses

The prognostic significance of individual MMP mRNA levels in ovarian cancer was evaluated using an online database.[8] The KM plotter (2017 version) is capable of investigating the effect of 54 675 genes on survival using 10 461 cancer samples, including 5143 breast, 1816 ovarian, 2437 lung and 1065 gastric cancer patients with a mean follow-up of 69, 40, 49 and 33 months, respectively.

In this database, gene expression data and overall survival information of 1816 patients with ovarian cancer were downloaded from the Gene Expression Omnibus, Cancer Biomedical Informatics Grid and The Cancer Genome Atlas cancer datasets.[8] Furthermore, the database offers clinical data, including histology, grade, stage, tumour protein p53 mutation status and treatment of ovarian cancer patients.

In brief, 23 *MMP* gene family members (*MMP1, MMP2, MMP3, MMP7–17,*

MMP19–21, and *MMP23–28*) were inputted into the database to get Kaplan–Meier survival plots.[8] Overall survival (OS) was selected as the survival endpoint. The expression cut-off points of the individual *MMP* genes were determined according to their median mRNA levels among the selected ovarian cancer samples. The patient samples were divided into two groups ('low' and 'high') according to established mRNA level cut-offs. The two patient cohorts were compared using the Kaplan–Meier survival plots and then hazard ratio (HR), 95% confidence intervals (CI) and log-rank *P*-values were calculated and depicted in a chart.

Human protein atlas database

Matrix metalloproteinase protein levels in normal ovary and ovarian cancer tissues was determined from the Human Protein Atlas database,[9] which includes immuno-histochemistry data from three cases of normal ovary and 12 cases of ovarian cancer tissues.

Results

There were 1656 patients with ovarian cancer in the database with available clinical data, including 1232 with serous ovarian cancer and 62 with endometrioid ovarian cancer. The median length of follow-up was 31.6 months (range, 1–242 months) and 930 patients had died at the end of follow-up. Initially, the prognostic value of the 23 *MMP* genes was evaluated for the 1656 patients with ovarian cancer using the KM plotter. High mRNA levels of MMP2 and MMP13 were demonstrated to be related to a worse OS in patients with ovarian cancer (HR 1.22, 95% CI 1.07, 1.38, *P* = 0.003; HR 1.16, 95% CI 1.02, 1.32, *P* = 0.021; respectively). However, high mRNA levels of MMP9, MMP10, MMP12 and MMP25 were associated

with a better OS in patients with ovarian cancer (HR 0.85, 95% CI 0.75, 0.97, *P* = 0.016; HR 0.87, 95% CI 0.77, 0.99, *P* = 0.038; HR 0.82, 95% CI 0.72, 0.93, *P* = 0.0027; HR 0.80, 95% CI 0.70, 0.91, *P* = 0.00051; respectively). The mRNA levels of the *MMP1*, *MMP3*, *MMP7*, *MMP8*, *MMP11*, *MMP14–21*, *MMP23*, *MMP24* and *MMP26–28* genes were not associated with OS in patients with ovarian cancer.

To further explore the correlation between individual MMPs and other clinicopathological features, the study investigated the correlation with histological subtype, pathological grade and clinical stage of patients with ovarian cancer (Table 1). High mRNA levels of MMP2 were correlated with a worse OS in serous ovarian cancer, while the mRNA levels of MMP9, MMP10, MMP12 and MMP25 were correlated with a better OS in serous ovarian cancer. With respect to endometrioid ovarian cancer, only MMP10 was associated with a worse OS. High mRNA levels of MMP9 and MMP12 were correlated with a better OS in patients with grade III ovarian cancer, but not in patients with grades I or II ovarian cancer. However, high mRNA levels of MMP13 were associated with a worse OS in patients with grades I and II ovarian cancer. With regard to clinical stage, high mRNA levels of MMP9, MMP10, MMP12 and MMP25 were associated with a better OS in patients with stages III + IV ovarian cancer, but not in patients with stages I + II ovarian cancer. However, high mRNA levels of MMP13 were associated with a worse OS in patients with stages I + II ovarian cancer.

The study then analysed the levels of selected MMP proteins (MMP2, MMP9, MMP10, MMP12, MMP13 and MMP25) in normal ovarian tissues (three cases) and ovarian cancer tissues (12 cases) using the Human Protein Atlas database. As shown in Figure 1a, stroma cells had low levels of

Table 1. Correlation of matrix metalloproteinase (MMP) mRNA levels with overall survival in patients with ovarian cancer stratified according to their clinicopathological characteristics.

Characteristic	MMP2 HR (95% CI), P-value	MMP9 HR (95% CI), P-value	MMP10 HR (95% CI), P-value	MMP12 HR (95% CI), P-value	MMP13 HR (95% CI), P-value	MMP25 HR (95% CI), P-value
Histological subtype						
Serous	1.29 (1.10, 1.50), $P = 0.001$	0.78 (0.67, 0.91), $P = 0.002$	0.78 (0.66, 0.92), $P = 0.003$	0.71 (0.61, 0.83), $P < 0.001$	1.12 (0.97, 1.31), NS	0.73 (0.61, 0.87), $P < 0.001$
Endometrioid	0.00 (0.00, Inf), NS	3.3 (0.55, 19.75), NS	5.84 (0.97, 35.32), $P = 0.03$	0.27 (0.04, 1.60), NS	4.52 (0.51, 40.47), NS	5.61 (0.58, 46.25), NS
Pathological grade						
Grade I	1.81 (0.66, 4.97), NS	0.90 (0.34, 2.34), NS	0.47 (0.17, 1.25), NS	1.34 (0.53, 3.4), NS	2.77 (0.99, 7.8), $P = 0.043$	1.32 (0.50, 3.49), NS
Grade II	1.14 (0.84, 1.54), NS	0.98 (0.72, 1.32), NS	0.82 (0.61, 1.11), NS	0.81 (0.60, 1.10), NS	1.39 (1.02, 1.88), $P = 0.035$	0.89 (0.66, 1.20), NS
Grade III	1.09 (0.92, 1.28), NS	0.76 (0.65, 0.90), $P = 0.001$	0.93 (0.79, 1.09), NS	0.71 (0.60, 0.84), $P < 0.001$	1.05 (0.89, 1.24), NS	0.87 (0.74, 1.02), NS
Clinical stage						
Stages I + II	0.98 (0.45, 2.13), NS	1.05 (0.49, 2.27), NS	0.92 (0.42, 2.00), NS	0.73 (0.33, 1.59), NS	3.24 (1.39, 7.56), $P = 0.004$	0.69 (0.31, 1.54), NS
Stages III + IV	1.11 (0.96, 1.29), NS	0.84 (0.72, 0.97), $P = 0.018$	0.83 (0.71, 0.96), $P = 0.012$	0.77 (0.66, 0.89), $P < 0.0001$	1.04 (0.90, 1.21), NS	0.85 (0.74, 0.99), $P = 0.037$

Kaplan–Meier survival plot comparison.

HR, hazard ratio; CI, confidence interval; Inf, infinite; NS, no significant association with overall survival ($P \geq 0.05$).
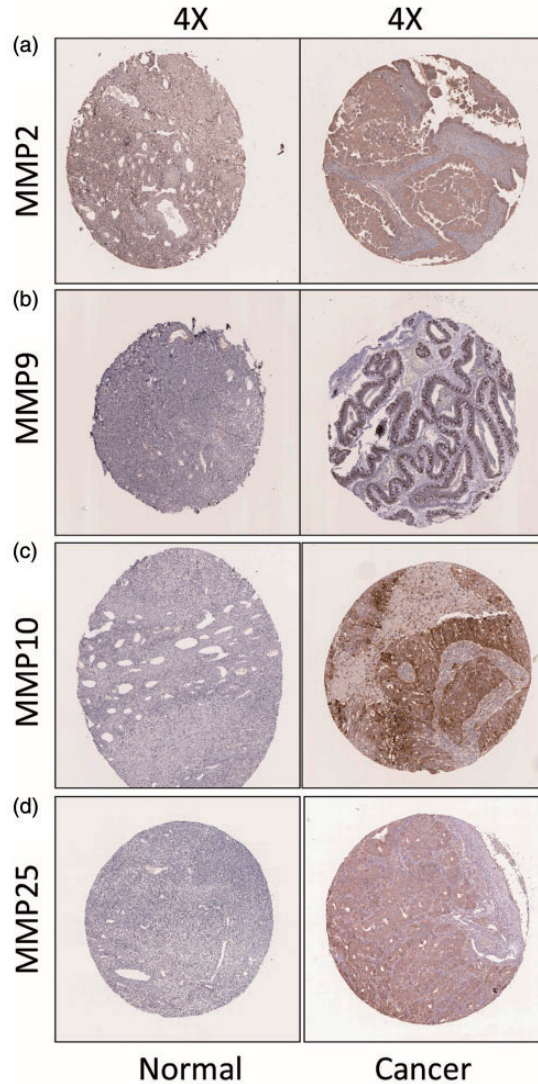
Figure 1. Comparison of the protein levels of matrix metalloproteinases (MMPs) in normal ovarian tissues and ovarian cancer tissues. The levels of (a) MMP2, (b) MMP9, (c) MMP10 and (d) MMP25 protein in normal ovary and ovarian cancer tissues were analysed using the Human Protein Atlas database. The colour version of this figure is available at: http://imr.sagepub.com.

MMP2 staining in normal ovarian tissues. In comparison, among the 12 cases of ovarian cancer tissues that were examined, medium levels of staining of MMP2 were detected in five cases, while the remaining seven cases had low levels of MMP2 staining. For MMP9, stroma cells had no staining in normal ovarian tissues, while there were three cases with high levels of MMP9 staining among the 12 ovarian cancer tissues that were examined (Figure 1b). For MMP10, stroma cells presented no staining in normal ovarian tissues. Using the same antibody, there were

four cases of high, one case of medium and three cases of low levels of MMP10 staining among the 12 ovarian cancer tissues that were examined (Figure 1c). Considering MMP25, stroma cells had no MMP25 staining in normal ovarian tissues. In comparison, among the 12 ovarian cancer tissues that were examined, there were three cases of medium and five cases of low levels of MMP25 staining (Figure 1d). No staining of MMP13 and MMP12 was detected in either normal ovarian tissues or ovarian cancer tissues.

Discussion

Matrix metalloproteinases have been associated with cancer for more than 40 years and the notion that MMP-mediated extracellular matrix degradation leads to cancer cell invasion and metastasis has been a guiding principle in MMP research.[10]

Higher levels of MMP2 in cancer cells have been reported in advanced ovarian cancer compared with their benign or pre-malignant counterparts.[11] To further investigate its prognostic significance among patients with ovarian cancer, a comprehensive review of eight studies that included 965 patients reported that those with positive tumour-derived MMP2 expression showed a worse prognosis compared with those with negative tumour-derived MMP-2 expression.[12] Similarly, a meta-analysis showed that MMP2 overexpression in tumour cells was significantly associated with a poor prognosis in patients with epithelial ovarian cancer.[13] Consistent with previous studies,[12,13] the current results showed that high levels of MMP2 mRNA were associated with a worse OS for all patients with ovarian cancer, particularly for those with serous ovarian cancer. Furthermore, the current results using the Human Protein Atlas database showed that MMP2 protein expression was elevated in ovarian cancer tissues compared with

normal ovarian tissue, which further demonstrated that this gene may be a poor prognostic indicator for patients with ovarian cancer.

With regard to MMP9, numerous studies have reported a relationship between MMP9 levels and clinical outcome among patients with ovarian cancer, however, the results have been controversial.[14,15] For example, MMP9 has been shown to play two roles in tumour progression, acting as a tumour promoter when expressed in the stroma while preventing tumour development when expressed in the epithelium.[14,15] In a homogeneous cohort of women with high-grade serous ovarian carcinoma, increased MMP9 tissue levels, as assessed by automated immunostaining quantification, were associated with a higher risk of death.[14] However, another study reported that expression of MMP9 had no prognostic relevance in patients with advanced epithelial ovarian cancer.[15] In the present study, the results demonstrated increased MMP9 protein levels in ovarian cancer tissues compared with normal ovarian tissues, which was consistent with the previous study.[14] However, with regard to its prognostic value among patients with ovarian cancer, the current study found that elevated MMP9 mRNA levels were associated with a favourable prognosis for all patients with ovarian cancer, in particular those with serous ovarian cancer. Higher levels of MMP9 mRNA predicted a better OS in grade III and stages III + IV ovarian cancers, but not in grades I + II and stages I + II ovarian cancers, suggesting it is a favourable prognostic indicator especially for late-stage and poorly differentiated ovarian cancers. This discrepancy between studies may be partly attributable to different patient populations, detection methods, mRNA level cut-offs and source regions due to the data being collected from several databases. Thus, it will be necessary to undertake more larger-scale, multicentre,

high-quality studies to precisely assess the relationship between MMP9 mRNA levels and prognosis of ovarian cancer.

There has been limited published research on the association between MMP10 and the prognosis of cancer. MMP10 has been reported to be overexpressed in colon cancer tissues and was shown to be an independent adverse prognostic marker among patients with colon cancer.[16] The current results showed elevated MMP10 protein levels in ovarian cancer tissues compared with normal ovarian tissue, which was consistent with the previous report in colon cancer.[16] These current findings also showed that higher mRNA levels of MMP10 were associated with a better OS for all patients with ovarian cancer, in particular in those with stages III + IV but not stages I + II, indicating that it may be a positive prognostic biomarker for late-stage ovarian cancer.

Matrix metalloproteinase-12 is involved in many pathological processes including cancer and it plays an essential role in invasion and metastasis of tumour cells.[17–19] Increased expression of MMP12 was observed in certain types of cancer, such as gastric cancer,[17] lung adenocarcinoma,[18] nasopharyngeal carcinoma[19] and cutaneous melanoma.[20] Knockdown of MMP12 inhibited proliferation and invasion of lung adenocarcinoma as well as nasopharyngeal carcinoma.[18,19] MMP12 was not only involved in cancer development and progression, but it also contributed to patient survival. For example, patients with cutaneous melanoma or gastric cancer with high levels of MMP12 tended to have an unfavourable OS compared with those patients with low levels of MMP12.[17,20] To the best of our knowledge, this is the first report investigating the relationship between MMP12 and the prognosis of ovarian cancer. In this current study, the results showed that higher mRNA levels of MMP12 were significantly correlated with a better OS for patients with serous ovarian cancer. Furthermore, this current study found that MMP12 mRNA levels predicted an improved OS in grade III and stages III + IV ovarian cancer, but not in grades I + II and stages I + II, suggesting that this gene is a favourable prognostic indicator especially among late-stage and poorly differentiated ovarian cancers.

Matrix metalloproteinase-13 plays essential roles in tumour angiogenesis, invasion and metastasis by degrading extracellular matrix and various collagens.[21,22] Although the prognostic role of MMP13 varies in different types of cancers,[21–24] the majority of studies reported that MMP13 gene expression predicted a poor clinical outcome in malignancies. For example, high levels of MMP13 were associated with a poor prognosis in salivary gland cancer,[23] non-small cell lung cancer,[24] invasive breast cancer,[25] gliomas,[26] oral squamous cell carcinoma[27] and colorectal cancer.[28] To date, there have not been any reports on the association between MMP13 and the clinical prognosis in patients with ovarian cancer. Consistent with the previous studies, these current results showed that high MMP13 mRNA levels were associated with a poor OS in patients with ovarian cancer.

Matrix metalloproteinase-25, one of the two glycosylphosphatidylinositol-anchored matrix metalloproteinases, plays a crucial role in pericellular proteolysis.[29] The biological functions of MMP25 in malignancies still remain to be elucidated. Elevated MMP25 mRNA levels were reported in gastric cancer[30] and colon cancer.[29] To date, there have not been any reports on the association between MMP25 and clinical prognosis in patients with ovarian cancer. In the present study, the results showed increased MMP25 protein levels in ovarian cancer tissues compared with normal ovarian tissues. The current study also found that MMP25 mRNA levels were correlated with an

improved OS among patients with ovarian cancer, in particular in those patients with serous ovarian cancer and stages III + IV ovarian cancer.

In conclusion, these current findings demonstrated that high mRNA levels of MMP2 and MMP13 were correlated with a worse OS for patients with ovarian cancer, while high mRNA levels of MMP9, MMP10, MMP12 and MMP25 were associated with a better OS in patients with ovarian cancer. These results suggest that the MMP family plays an important prognostic role in ovarian carcinoma. Our further studies will validate these results at the protein level in human ovarian cancer samples and explore the clinical application of the *MMP* gene family in ovarian cancer prognosis and treatment.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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