

Original Research

Prognostic value of matrix metalloproteinase 2 protein expression in ovarian cancer is age- and stage-dependent

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Abstract

Objective: Matrix metalloproteinase 2 (MMP2) has been associated with tumor development and invasion; however, the information available regarding its prognostic value in ovarian cancer (OC), especially in the Arabian Peninsula, is limited. The aim of this retrospective study was to analyze MMP2 protein expression and assess its prognostic value. **Methods:** In total, 245 formalin-fixed and paraffin-embedded (FFPE) primary OC tissue samples were randomly collected from patients with available clinicopathological data, including disease of all stages and all histological subtypes. MMP2 protein expression was measured using automated tissue microarray and immunohistochemistry techniques. Statistical analyses were performed using SPSS, with $p < 0.05$ considered statistically significant. **Results:** Cytoplasmic MMP2 protein expression patterns were higher in 53% of all tumor samples. The MMP2 expression profile was not significantly correlated with most clinicopathological features including age, tumor site, size, grade, and lymph node status ($p > 0.05$). However, when adjusted according to the disease stage or patient age, MMP2 overexpression showed a significant indication of a poor outcome and recurrence as evaluated using univariate Kaplan–Meier analysis for disease-free survival (DFS) ($p = 0.04$ and $p = 0.03$, respectively, log-rank test), but not for disease-specific survival (DSS) ($p > 0.05$, log-rank test). **Conclusion:** This study showed that MMP2 protein overexpression was a negative prognosticator in Saudi OC patients with advanced stage and/or young age. These results could pave the way towards more effective and personalized detection, prognosis, and management of OC.

Keywords: Ovarian cancer; Matrix metalloproteinase; MMP2; Prognosis; Tissue microarray; Age; Stage

1. Introduction

Precision oncology is a new discipline launched after the completion of the Human Genome Project that aims to enhance treatment outcomes through accurate molecular stratification of cancer patients [1]. Despite the huge efforts that have been made, Precision oncology is not implemented in daily clinical routine yet [1,2]. This is particularly important in ovarian cancer (OC), which is characterized by higher complexity and heterogeneity at the molecular, genetic, and phenotypic levels [2]. The advent of precision technologies and the subsequent emergence of molecular and genetic data have significantly increased our understanding of OC heterogeneity. Clinically, most women newly diagnosed with OC unfortunately have advanced stage disease (III and IV), where the cancer has

spread to the upper abdomen or beyond the peritoneal cavity. Despite their response to surgery and chemotherapy, these patients have a dismal survival rate because they often develop subsequent recurrence [3–5]. In the United States, OC accounts for 5% of cancer deaths among women, more than any other gynecologic cancer. In the Kingdom of Saudi Arabia, OC is one of the main cancers affecting women, accounting for 3.2% of all cancers [6–8]. Most OCs are typically epithelial in origin and are frequently diagnosed at an advanced stage of the disease. This is mainly due to the asymptomatic nature of early OC combined with a lack of sensitive biomarkers for detecting OC at this critically important stage. In early stage disease, the recognized signs and symptoms are indistinguishable, vague, and non-specific, which minimizes the chances of early diagnosis



[9]. Most patients present with advanced metastatic disease at the time of diagnosis [10]. Although significant progress has been made in our understanding of OC biology, sensitive and reliable early diagnostic and prognostic tools are still lacking. Therefore, identifying new molecular mechanisms of OC prognosis and/or progression is crucial for the timely detection and treatment of this disease.

The standard OC management approach includes tumor removal (cytoreductive) surgical resection followed by adjuvant therapy. However, numerous clinical and pathophysiological factors influence the overall treatment outcome. These include age, stage, and grade, which have been reported to be correlated with OC patient survival outcomes (disease-free survival [DFS], disease-specific survival [DSS], and overall survival [OS]) [11,12]. Among the numerous clinicopathological features, stage, grade, and lymph node status have been suggested as OC prognosticators [13]. The prognosis was reported to be poor, with a mean five-year survival period of only 44% for patients with OC [14]. However, the outcomes were not as expected, especially for patients with the same disease stage and/or receiving the same treatment regimen [15]. Therefore, finding an effective molecular screening technique/approach that allows the early detection of OC and prognosis prediction continues to be a challenging aspect of cancer biology [16,17].

The progression of OC involves an array of coordinated complex molecular processes leading to metastatic spread, ultimately influencing the survival rate of patients. The metastatic process is a complex cascade of interactions among tumor cells, leading to the degradation of the extracellular membrane (ECM) and basement membranes. The degradation of these membranes is mediated by specific protease enzymes called matrix metalloproteinases (MMPs), a large family of membrane-type secreted proteases. MMP2 is a member of the MMP family and has been reported to play a vital role in cancer cell invasion and migration through the degradation of the basement membrane and components of the ECM, including collagen, fibronectin, and elastin [18]. MMP2 expression has been shown to correlate with higher grades of disease and metastatic spread of solid tumors, including gynecological cancer [19–22]. The expression of MMP2 in tumor cells was reported to be significantly higher in the advanced stages of OC than in their benign or premalignant counterparts [23]. Moreover, the upregulation of MMP2 expression through the extracellular signal-regulated kinase (ERK) pathway was reported to be associated with OC invasion, angiogenesis, and metastasis [24–28]. The expression of MMP2 protein in OC tissues has also been reported as an indicator of poor prognosis and was found to be significantly associated with distant metastasis [28,29]. Furthermore, inhibition of the MMP2 upstream pathways has been suggested as a potential therapeutic target to suppress OC proliferation and invasion [30,31]. These findings sug-

gest that MMP2 may be an effective prognosticator in patients with OC. Therefore, this study was designed to analyze MMP2 protein expression patterns and to investigate its prognostic value in a cohort of patients with OC from Saudi Arabia. The current study is expected to enhance our understanding of the molecular events determining OC prognosis.

2. Patients and methods

2.1 Patients

The study included a cohort consisting of 245 formalin-fixed and paraffin-embedded (FFPE) tissue samples of primary ovarian cancer (OC) collected between 1995 and 2004 and archived at the Pathology Department, King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia. All consenting patients with OC, including all stages and all histological subtypes, with available clinicopathological data and FFPE blocks converted to tissue microarray (TMA) slides were randomly included in the study. Patients who received neoadjuvant therapy were excluded from the study cohort. Furthermore, only specimens consisting of more than 80% tumor cells were used for analysis. The histopathological features of carcinoma specimens were classified according to the tumor node metastasis (TNM) classification system. The mean follow-up time for the cohort was 62 months. During patient follow-up, recurrence was suspected whenever any clinical signs and symptoms were reported, and confirmed using both computed tomography (CT) and CA-125 analysis. All clinical and pathological data were collected from the patients' medical records. This study was approved by the ethical committee of King Abdulaziz University Hospital (reference number: KAUH-189-14).

2.2 Tissue microarray

Using a TMA technique [32], we successfully transferred 245 blocks of OC to construct TMA slides to evaluate the expression of MMP2 protein. Our TMA slides were previously validated for copy number variations in bladder and colorectal cancers [33–35]. TMA is a reliable and cost-effective technique for biomarker discovery and validation in solid tumors.

2.3 Immunohistochemistry (IHC)

Overexpression of MMP2 protein was detected using an automated IHC protocol with the iView DAB Detection Kit (Ventana) on a BenchMark XT automated staining system (Ventana). The protocol included the following steps: deparaffinization, heat pretreatment, antigen retrieval, and incubation with the anti-MMP2 primary rabbit monoclonal antibody (MMP2-507; Lot# 6000363; Leica Systems). The slides were counterstained with hematoxylin II and bluing reagent (Ventana). Slides were removed from the automated immunostainer and rinsed with mild detergent and water to remove any residual buffer or liquid coverslip so-

lution. The slides were then immersed in serial ethanol solutions (70%, 95%, and 100% concentration). Finally, one drop of Tissue-Tek glass mounting medium was applied to each slide before placing a coverslip.

2.4 Evaluation of MMP2 expression pattern

IHC MMP2 protein expression in all OC samples was evaluated blindly by two independent expert pathologists without any prior knowledge about the patients/samples/clinical features. The expression patterns were assessed using a regular Nikon light microscope at 40× magnification. The intensity of IHC staining was divided into four categories: (0), no/negative expression; (1+), weak expression; (2+), moderate expression, clearly positive but still weak; and (3+), strong MMP2 expression. Both intensity and the fraction of positively stained cells were used to calculate the staining index score using the following formula: $I = 0 \times f_0 + 1 \times f_1 + 2 \times f_2 + 3 \times f_3$; where (I) is the staining index and (f_0 to f_3) are the fractions of the cells showing a level of staining intensity (from 0 to +3), based on a previously validated method designed by Lipponen and Collan [36] and used later by our group [37].

2.5 Statistical analysis

Statistical analyses were performed using SPSS® (IMB, NY, USA) software package (PASW Statistics for Windows, version 19). Frequency tables were analyzed using the chi-squared test, with the likelihood ratio (LR) or Fischer's exact test to assess the significance of the correlation between the categorical variables. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were calculated where appropriate, using the exact method. DSS and DFS were calculated as the time from diagnosis to death (due to disease) or to the date of last seen alive, and time from diagnosis to the appearance of recurrent disease or date of last seen disease-free, respectively. When calculating DSS, patients who died of other or unknown causes were censored. The univariate analysis of DSS and DFS outcomes was based on the Kaplan–Meier method with log-rank (Mantel–Cox) comparison test. Statistical significance was set at $p < 0.05$.

3. Results

Our cohort analysis showed that 56% of the patients were more than 50 years old, and more than 73% had bilateral OC. The tumor size was larger than 10 cm in 51% of patients, while 68% of the cohort had high-grade tumors. Data analysis also showed that the majority of patients (63%) did not use oral contraceptives. Notably, most of the patients (58%) were premenopausal. While the tumor was at a high stage in 63% of patients, recurrence was found only in 43% of patients. The results of all parameters are summarized in Table 1.

3.1 MMP2 protein expression patterns in ovarian cancer tissues

The frequency of the low and high MMP2 protein expression patterns in OC sections was analyzed. Generally, MMP2 expression showed cytoplasmic localization. Based on its protein expression intensity, MMP2 was classified into two categories: 53% of all tumors showed high MMP2 expression (2+, 3+), while 47% exhibited low MMP2 expression (0, 1+) (Fig. 1).

3.2 Correlation of IHC MMP2 protein expression with clinicopathological features

The correlation of MMP2 protein expression with patients' clinicopathological characteristics using the low (0, 1+) and high (2+, 3+) expression cut-off was the most powerful discriminator. The association between MMP2 expression and clinicopathological features is summarized in Table 1. Interestingly, no clinicopathological features significantly correlated with MMP2 expression ($p > 0.05$), except for the use of oral contraceptives ($p = 0.05$) (Table 1).

3.3 Correlations of MMP2 expression with survival outcomes in all patients

In the univariate (Kaplan–Meier) survival analysis, there was a trend of differences in favor of MMP2-negative/low expression patterns in which, MMP2-negative tumors had a non-significantly better DFS ($p = 0.1$, log rank; Fig. 2A) and DSS ($p = 0.5$, log rank, Fig. 2B).

3.4 Correlation of advanced stage-adjusted MMP2 expression with survival outcomes

When the survival outcomes of OC patients were analyzed in correlation with the adjusted tumor stage category (early [I, II] vs. advanced [III, IV] stages), the results showed a significant difference in favor of MMP2-negative/low expression pattern profiles (0, 1+) compared to MMP2-positive/high expression (2+, 3+) profiles. In fact, patients with OC tumors exhibiting MMP2 negative/low expression had a significantly favorable DFS ($p = 0.04$, log rank, Fig. 3A) and a tendency for favorable DSS ($p = 0.4$, log-rank test, Fig. 3B).

3.5 Correlations of young age-adjusted MMP2 expression with survival outcomes

Similarly, when we refined the focus on the young age-adjusted OC patients (age <50 years) in our cohort, a significantly favorable DFS ($p = 0.03$, log rank, Fig. 4) marked by lower recurrence rates was reported in young OC patients with low MMP2 protein expression.

3.6 Multivariate analysis

Multivariate Cox regression analysis revealed that advanced tumor stage ($p < 0.001$), and not MMP2 protein expression profile ($p = 0.45$), was an independent factor for poor survival in relation to patient age, lymph node status, tumor grade, and histological type.

Table 1. Correlation between MMP2 protein expression patterns and OC patients' clinicopathological parameters.

| Features | Number of cases (%) | MMP2 expression | | <i>p</i> -value |
|-------------------------|---------------------|-----------------|----------|-----------------|
| | | Low (%) | High (%) | |
| Age | | | | 0.837 |
| <50 years | 65 (56%) | 36 (31%) | 29 (25%) | |
| >50 years | 51 (44%) | 27 (23%) | 24 (21%) | |
| Tumor Site | | | | 0.639 |
| Right | 18 (16%) | 12 (10%) | 6 (5%) | |
| Left | 13 (11%) | 7 (6%) | 6 (5%) | |
| Bilateral | 85 (73%) | 44 (38%) | 41 (35%) | |
| Tumor stage | | | | 0.803 |
| Low stage | 34 (37%) | 24 (21%) | 19 (16%) | |
| High stage | 73 (63%) | 39 (34%) | 34 (29%) | |
| Tumor size | | | | 0.156 |
| 1–5 cm | 25 (22%) | 16 (14%) | 9 (8%) | |
| 6–10 cm | 31 (27%) | 12 (11%) | 19 (17%) | |
| >10 cm | 58 (51%) | 34 (30%) | 24 (21%) | |
| Grade | | | | 0.871 |
| Low grade | 15 (15%) | 9 (9%) | 6 (6%) | |
| Intermediate | 17 (17%) | 9 (9%) | 8 (8%) | |
| High grade | 68 (68%) | 38 (38%) | 30 (30%) | |
| LN* status | | | | 0.140 |
| Positive | 22 (33%) | 14 (21%) | 8 (12%) | |
| Negative | 44 (67%) | 20 (30%) | 24 (36%) | |
| Histological subtype | | | | 0.989 |
| Serous | 51 (46%) | 29 (26%) | 22 (20%) | |
| Mucinous | 26 (23%) | 15 (14%) | 11 (10%) | |
| Other types | 34 (31%) | 17 (15%) | 17 (15%) | |
| LVI* | | | | 0.564 |
| Positive | 41 (44%) | 22 (23%) | 19 (20%) | |
| Negative | 53 (56%) | 25 (27%) | 28 (30%) | |
| BMI* | | | | 0.962 |
| <23 kg/m ² | 7 (8%) | 3 (3%) | 4 (4%) | |
| 23–26 kg/m ² | 27 (29%) | 15 (16%) | 12 (13%) | |
| >26 kg/m ² | 58 (63%) | 32 (35%) | 26 (28%) | |
| Age at menarche | | | | 0.144 |
| <13 years | 21 (22%) | 7 (7%) | 14 (5%) | |
| >13 years | 73 (78%) | 38 (40%) | 35 (37%) | |
| Oral contraceptives | | | | 0.050 |
| Never-use | 52 (63%) | 28 (34%) | 24 (29%) | |
| Sometimes | 24 (29%) | 17 (21%) | 7 (9%) | |
| Ever-use | 6 (7%) | 1 (1%) | 5 (6%) | |
| Recurrence status | | | | 0.465 |
| No recurrence | 51 (57%) | 31 (34%) | 20 (22%) | |
| Recurrence | 39 (43%) | 18 (20 %) | 21 (23%) | |
| Endpoint status | | | | 0.554 |
| Living | 36 (35%) | 17 (16%) | 19 (18%) | |
| Deceased | 68 (65%) | 38 (37%) | 30 (29%) | |

*LN, lymph node; LVI, lymphovascular invasion; BMI, body mass index.

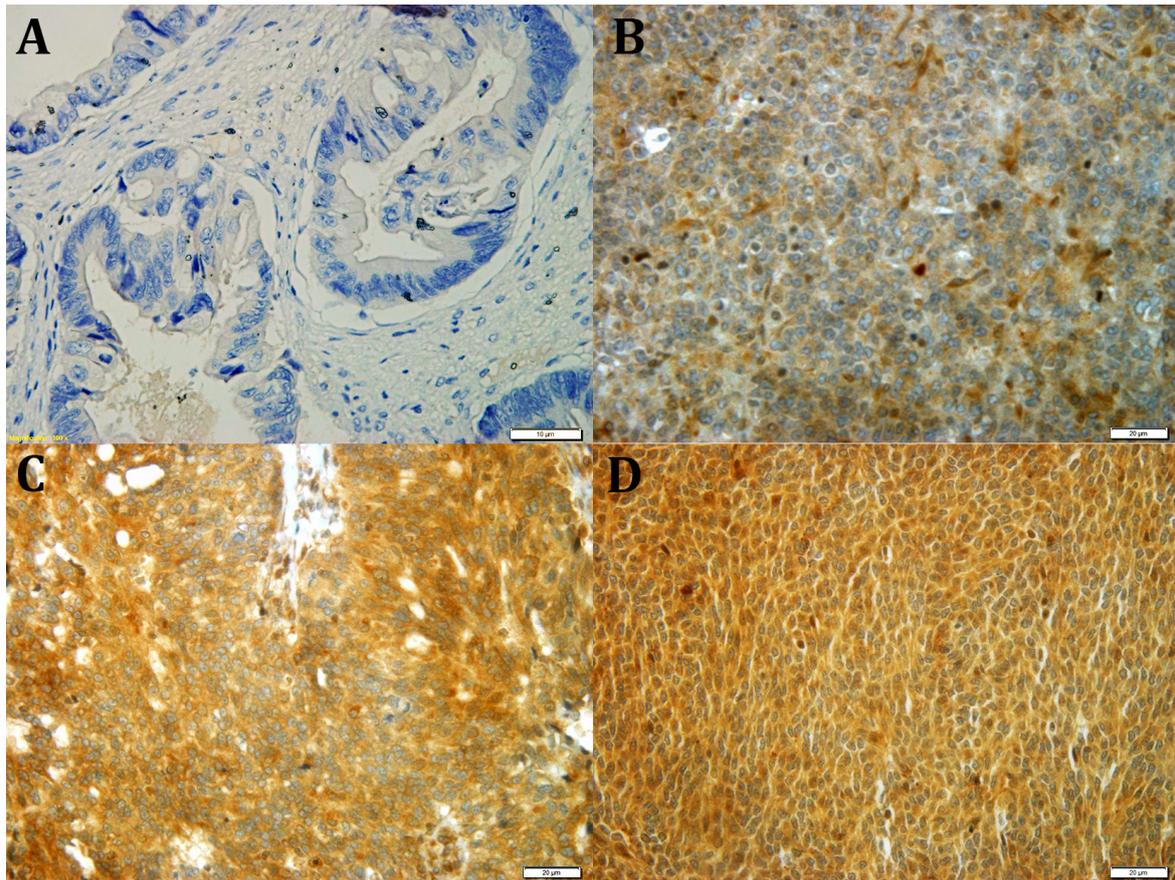


Fig. 1. Cytoplasmic MMP2 expression patterns. (A) No (0) expression. (B) Weak (1+) expression. (C) Moderate (2+) expression. (D) Strong (3+) expression of MMP2 protein. Magnification is $\times 40$.

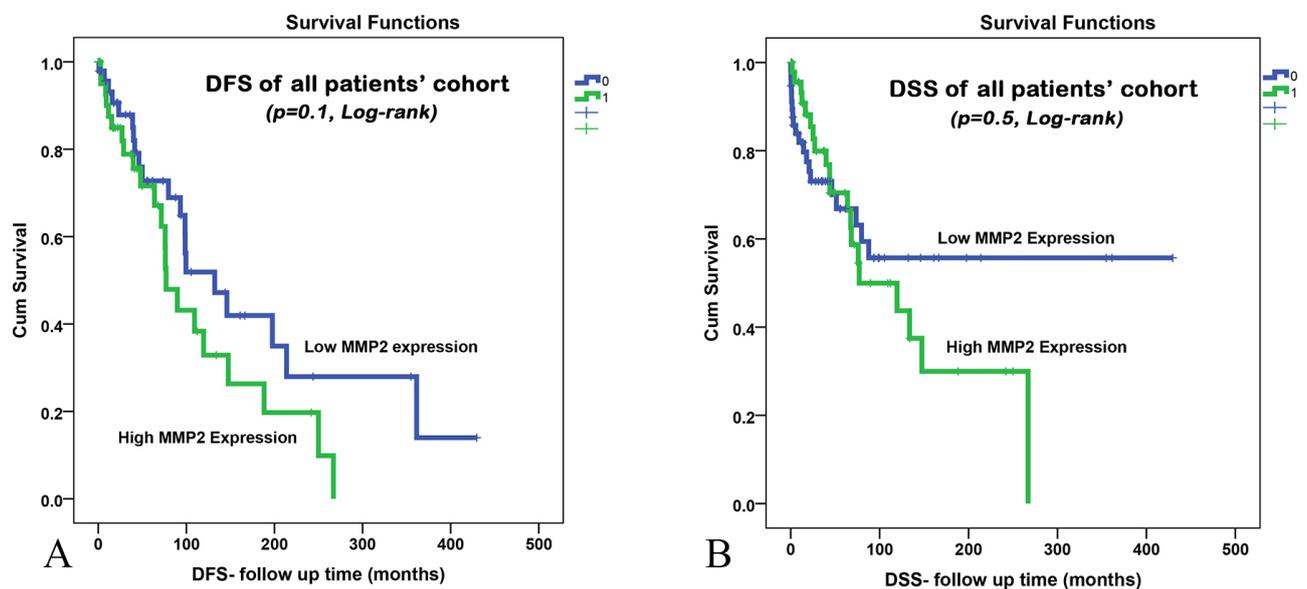


Fig. 2. Correlations of cytoplasmic MMP2 expression with survival outcomes in the whole OC cohort using low (0, 1+) vs. high (2+, 3+) MMP protein expression as a discriminator. (A) Cytoplasmic MMP2 protein expression pattern as a determinant of disease-free survival (DFS) in univariate (Kaplan–Meier) analysis, ($p = 0.1$, log rank). (B) Cytoplasmic MMP2 protein expression pattern as a determinant of disease-specific survival (DSS) in univariate (Kaplan–Meier) analysis, ($p = 0.5$, log rank).

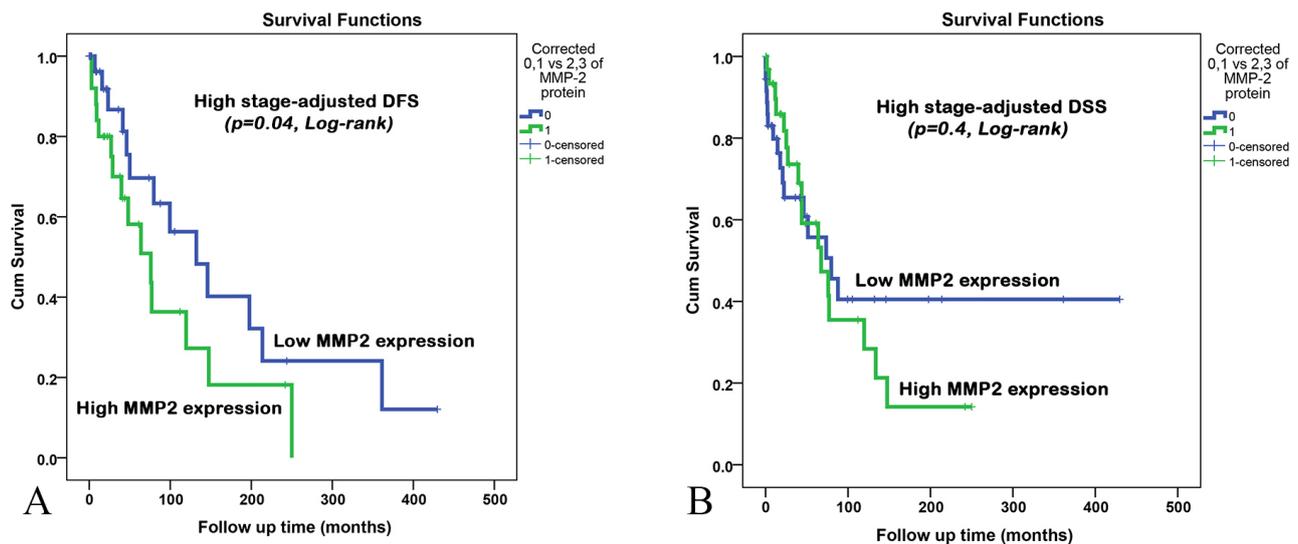


Fig. 3. Correlation of cytoplasmic MMP2 expression with survival outcomes patients with advanced stage (III, IV) OC using low (0, 1+) vs. (high (2+, 3+) MMP2 expression as a discriminator. (A) Cytoplasmic MMP2 protein expression pattern status as a determinant of disease-free survival (DFS) in univariate (Kaplan–Meier) analysis, ($p = 0.04$, log rank). (B) Cytoplasmic MMP2 protein expression pattern as a determinant of disease-specific survival (DSS) in univariate (Kaplan–Meier) analysis, ($p = 0.4$, log rank).

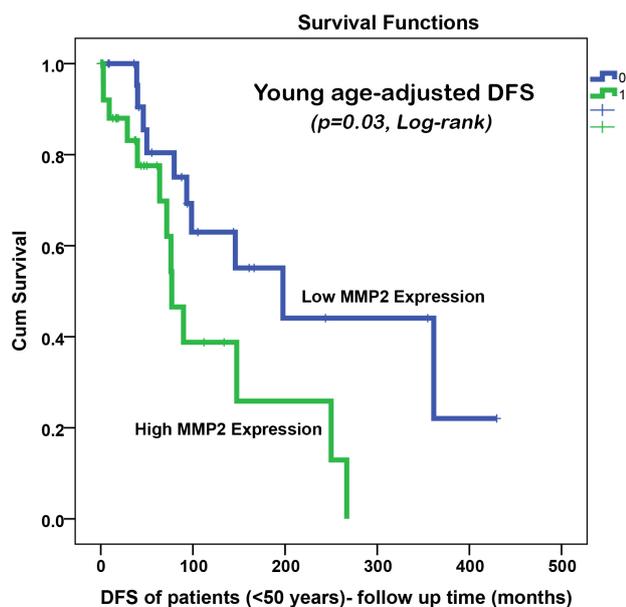


Fig. 4. Correlations of cytoplasmic MMP2 expression with survival outcomes in young OC patients (age <50 years) using low (0, 1+) vs. high (2+, 3+) protein expression as a discriminator as a determinant of disease-free survival (DFS) in univariate (Kaplan–Meier) analysis, ($p = 0.03$, log rank).

4. Discussion

Advanced precision oncology tools are used to enhance treatment outcomes through accurate molecular stratification of cancer patients. Therefore, the identification of more reliable molecular prognostic markers and clinicopathological factors is urgently required to improve strate-

gies for OC management and offer effective diagnostic services to patients [32,33]. Therefore, the main purpose of this study was to investigate MMP2 protein expression patterns in patients as a potential prognosticator of OC.

Interestingly, 56% of our OC cohort was younger than 50 years. In data released by Cancer Research UK, over half (53%) of women diagnosed with OC were ≥ 65 years old. Moreover, 50% of OC patients diagnosed with OC in the United States were aged ≥ 63 years [38]. These findings highlight a 13-to-15-year earlier onset of OC in our Saudi cohort. This important difference in the age of patients with OC in Saudi Arabia and the Arabian Peninsula from that in western countries is a serious challenge that requires further investigation.

Another interesting finding was that 63% of our OC cohort were overweight or obese with BMI > 26 kg/m², which is consistent with previous studies showing that obesity is an important risk factor for several cancers, including OC [39,40]. Although the intricate molecular mechanisms of obesity-driven risks are still poorly understood, accumulation of adipose tissue seems to induce androgen-dependent inflammation that could trigger OC initiation [41].

Our results showed a significant association between MMP2 expression and the use of oral contraceptives ($p = 0.05$). In fact, MMP2 expression was mainly lower in high-grade tumors as well as in patients who sometimes or ever used oral contraceptive pills. Since higher MMP2 expression is associated with worse prognosis and metastasis, these results are in agreement with previous studies showing that the sometimes/ever use of contraceptives lowered the risk of OC [42]. Oral contraceptives have been sug-

gested to confer protection against OC in women [43]. Furthermore, MMP2 expression was lower mainly in patients with an age of menarche >13 years, which might be related to less aggressive OC. These findings are in line with studies reporting an inverse correlation between age at menarche and OC risk [44].

Although MMP2 protein expression did not have significant correlations with the remaining clinicopathological features, including tumor grade and stage (Table 1), as reported elsewhere [45], associations with other diagnostic aspects were observed. For instance, approximately 63% of our cohort had advanced OC (III and IV), and more than 73% of the patients had bilateral OC (Table 1). Taken together, these findings indicate late OC diagnosis in Saudi Arabia. In fact, the hallmark of advanced disease is the extensive dissemination of OC cells to distant organs.

Numerous studies have suggested that aberrant MMP2 overexpression and function is an important marker to be investigated for its role in cancer invasion, migration, and metastasis, including OC [46,47], and hence could be a promising prognosticator in our OC cohort.

In the Kaplan–Meier survival analysis, both the DFS and DSS analysis of all our patient cohorts did not reveal significant correlations between MMP2 expression and survival outcomes ($p = 0.1$ and $p = 0.5$ respectively, log-rank test) (Fig. 2A,B). However, a general tendency was observed for both DFS and DSS where OC patients with low MMP2 expression (0, 1+) had better recurrence and survival outcomes than those with high MMP2 expression (2+, 3+).

We then refined the analysis by focusing mainly on patients with advanced stage OC, since they are the most vulnerable population of the cohort. Strikingly, MMP2 protein expression was a significant prognosticator of advanced-stage-adjusted (III, IV) OC patients' recurrence (DFS) ($p = 0.04$, log-rank) (Fig. 3A). In fact, at more than 10 years of follow-up of patients with advanced stage OC, only 42% of patients with OC with both advanced-stage tumors and low MMP2 protein expression (0, 1+) experienced recurrence compared to 63% of patients with MMP2 overexpression during the same period. For advanced stage disease, the tendency for favorable DSS was more pronounced but remained insignificant with potential prognosis after 5 years ($p = 0.4$, log-rank) (Fig. 3B). These findings support that MMP2-negativity/low expression in OC was a good general prognosticator in our patient cohort, mainly in those with advanced stage disease, and support MMP2 involvement in key molecular events that promote OC metastatic progression and recurrence, as suggested elsewhere [48].

Additionally, we focused on young OC patients (age <50 years) in our cohort to explore the early onset of OC in KSA and the Arabian Peninsula discussed earlier. Remarkably, lower MMP2 expression showed a stronger prognostication of recurrence (DFS) in young patients with OC after age adjustment ($p = 0.03$, log-rank) (Fig. 4). At 10 years

of follow-up, 62% of young patients (age <50 years) with MMP2 overexpression experienced OC recurrence compared to only 37% of those with low MMP2 expression.

Taken together, these findings showed that when patients with OC were divided according to having advanced stage disease or their young age, MMP2 protein expression showed significant prognostic value. In patients with advanced stage disease (III, IV) or at a younger age (age <50 years), lower MMP2 protein expression was more likely to behave better, have lower recurrence/relapse, and survive longer with and/or without the disease. These results are in line with previous studies in which MMP2 protein overexpression was reported to be associated with poor prognosis in OC patients [49]. MMP2 was also reported to be the main DFS prognosticator in epithelial OC (EOC) and has been suggested to be involved early in the OC invasion process [50]. Similarly, Wang *et al.* [51] showed that MMP2 expression was significantly higher ($p < 0.05$) in OC tissues with metastasis (advanced stages) than in those without metastasis (early stages), but did not correlate with age. Other studies reported that MMP2 overexpression was also suggested as a prognosticator of DSS in OC and associated with the presence of particularly aggressive OC clones, invasiveness, and disease progression [48,52]. In fact, metastasis in OC is a complex multistep process that has been reported to be mediated by different cellular proteolytic enzymes, including MMPs [53]. MMPs are a large family of calcium-dependent zinc-containing endopeptidases capable of degrading a variety of protein components of the ECM, which is the primary barrier to tumor metastasis [54–56]. Among all MMPs, MMP2, in particular, has been shown to be a highly efficient metalloproteinase that degrades ECM components, mainly native collagen types IV and V, entactin, fibronectin, and elastin, thereby promoting stromal invasion and distant dissemination to other organs [47,57]. In line with our finding that MMP2 protein expression correlated with survival in advanced stage disease, studies have also demonstrated that MMP2 is more highly expressed in the cystic fluid of both serous and mucinous OC than in benign OC [58]. The higher expression of MMP2 in OC cells is significantly related to an increased risk of death among patients with OC and predicts poor prognosis [59]. This MMP2-induced extracellular proteolysis in OC through degradation of the main components of the ECM and basement membrane, primarily type IV collagen, vitronectin, and fibronectin, was suggested to disturb tissue homeostasis, which in turn promotes tumor growth, inflammation, and tissue invasion [47,60,61]. This prometastatic effect of MMP2 seems to disrupt the ECM structure, allowing tumor cells to proliferate, detach from their primary site, and invade other tissues [62].

Although studies are unanimous about the poor prognosis of patients with MMP2 overexpression in malignant tissues, the prognostic value of MMP2 stromal expression remains controversial [50,63,64]. Additionally, the up-

stream downregulation of MMP2 expression in OC cell lines in different ways reduces or inhibits cell proliferation and invasion *in vitro* [60].

Taken together, our results and the findings of these studies confirm the prognostic value of MMP2 mainly in patients with advanced stage disease and who are younger. They also highlighted the need for additional comprehensive studies using large cohorts of OC patients to further validate these findings and investigate both epithelial and stromal MMP2 expression in OC to elucidate their functional interactions, assess their prognostic value, and investigate potential therapeutic targets of this promising biomarker.

5. Conclusions

This study found an interesting advanced stage-adjusted and young age-adjusted prognostic value of MMP2 protein expression in OC. Therefore, the outcomes of this study will be useful to inform patients of their prognosis and to recommend more intensive follow-up in patients with higher MMP2 expression (poor prognosis). These findings suggest that MMP2 is a potential prognostic marker for OC that requires future validation studies to design effective strategies for prognosis and effective disease management.

Abbreviations

ASCO, American Society of Clinical Oncology; BMI, body mass index; CAP, College of American Pathologists; DFS, disease-free survival; DSS, disease-specific survival; ECM, extracellular membrane; EOCs, epithelial ovarian carcinomas; ERKs, extracellular signal-regulated kinases; FFPE, formalin-fixed and paraffin-embedded; IARC, International Agency for Research on Cancer; IHC, immunohistochemistry; KAUH, King Abdulaziz University Hospital; LN, lymph node; LR, likelihood ratio; LVI, lymphatic vascular invasion; MMP2, human matrix metalloproteinase 2; OC, ovarian cancer; OR, odds ratios; OS, overall survival; TMA, tissue microarray; TNM, tumor, node, and metastasis.

Author contributions

MA, AB, and KS—study design, statistical analysis, and manuscript drafting; MAJ, MAE, MR, and AEO—data analysis, and results and discussions drafting; JAM, NA, HS, and HB—TMA design and construction, immunostaining and manuscript revision; SS, HC, MS, and SM—clinicopathological data collection, statistical analysis, and manuscript critical proofreading; KS and MA—study design and supervision of the whole team. All authors critically reviewed and agreed with the final version of the manuscript.

Ethics approval and consent to participate

The FFPE samples were collected and used after obtaining informed consent, and according to the guidelines and approval of the Ethical Committee of the King Abdulaziz University Hospital under reference number KAUH-189-14.

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Conflict of interest

The authors declare no conflict of interest.

Contribution to the field statement

This study reported the potential prognostic value of MMP2 protein expression in OC patients, mainly in those with advanced disease and/or who are younger. To the best of our knowledge, this is the first study in the Arabian Peninsula to investigate this promising biomarker towards the identification of effective strategies for better prognosis and management of OC patients.

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