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Increased expression of MMP17 predicts poor clinical outcomes in epithelial ovarian cancer patients

Chao Xiao, MS[a,b], Yao Wang, BS[a], Qijun Cheng, BS[a,*], Yuchao Fan, MD[c]

Abstract

Ovarian cancer has the highest fatality rate among female reproductive system cancers, which is due to lack of biomarker for diagnosis and prognosis. We aimed to evaluate the role of matrix metalloproteinase 17 (MMP17) in ovarian cancer tumorigenesis and prognosis. Based on the epithelial ovarian cancer (EOC) in The Cancer Genome Atlas database, we determined the expression of MMP17 using the Wilcoxon rank-sum test. The biological functions of MMP17 were evaluated using the Metascape database and Gene Set Enrichment Analysis. The association between MMP17 and immune cell infiltration was investigated by single sample Gene Set Enrichment Analysis. Logistic analysis was applied to study the correlation between MMP17 expression and clinicopathological characteristics. Finally, Cox regression analysis, Kaplan–Meier analysis, and nomograms were used to determine the predictive value of MMP17 on clinical outcomes in EOC patients. The expression of MMP17 was much higher in EOC patients than in pericarcinomatous tissues ($P < .001$). MMP17-associated differentially expressed genes were significantly enriched in cell extracellular matrix (ECM) degrading and corresponding pathways in the high MMP17 expression phenotype. MMP17 has a high sensitivity and specificity for EOC diagnosis, with an area under the curve of 0.988. MMP17 expression was found to be an independent risk factor for overall survival (hazard ratio [HR]: 1.488, $P < .001$), progression-free interval (HR: 1.347, $P < .01$), and disease-specific survival (HR: 1.548, $P < .01$). Increased MMP17 expression in EOC may contribute to carcinogenesis by degrading ECM and provide diagnostic and prognostic value for clinical outcomes.

Abbreviations: CESC = cervical squamous cell carcinoma and endocervical adenocarcinoma, CR = complete response, DEGs = differentially expressed genes, DSS = disease-specific survival, ECM = extracellular matrix, FIGO = Federation International of Gynecology and Obstetrics, GSEA = Gene Set Enrichment Analysis, HR = hazard ratio, IQR = interquartile range, K–M = Kaplan–Meier, NES = normalized enrichment score, OS = overall survival, PAAD = pancreatic adenocarcinoma, PD = progressive disease, PFI = progression-free interval, PR = partial response, PRAD = prostate adenocarcinoma, RD = radical resection, READ = rectum adenocarcinoma, SD = stable disease, SKCM = skin cutaneous melanoma, TCGA = The Cancer Genome Atlas, THCA = thyroid carcinoma, UCEC = Uterine Corpus Endometrial Carcinoma.

Keywords: bioinformatics analysis, matrix metalloproteinases17, ovarian cancer, prognosis

1. Introduction

Ovarian cancer is a life-threatening malignant tumor for women all over the world, with the third highest incidence and the highest fatality rate among female reproductive system cancers.[1] The 5-year survival rate for advanced ovarian cancer is between 30% and 40%.[2] Advanced diagnosis and platinum resistance are responsible for the poor prognosis of ovarian cancer. Epithelial ovarian cancer (EOC) is the most prevalent histological subtype of ovarian cancer, accounting for 90 percent or more of all cases, and it has distinct genetic features that can help enhance the accuracy and efficacy of treatment.[3,4] This makes the discovery of novel biomarkers for early detection and prediction of ovarian cancer invasion and metastasis extremely helpful.

The destruction of extracellular matrix (ECM) is required for malignant invasion and metastasis. Matrix metalloproteinases (MMPs) are a huge family of calcium-dependent zinc-containing endopeptidase that may break down almost any extracellular matrix to accelerate the tumor invasion and metastasis.[5–7] Upregulation of MMP2, MMP9, and MMP14 has been linked to an increased risk of ovarian cancer.[7,8] Matrix metalloproteinase 17 (MMP17) is a membrane-type specific MMP that interacts

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1

Clinical characteristics of the EOC patients based on TCGA.

Characteristic	Level	Low expression of MMP17 (n = 189)	High expression of MMP17 (n = 190)
FIGO stage, n (%)	Stage I	1 (0.3)	0 (0)
	Stage II	11 (2.9)	12 (3.2)
	Stage III	145 (38.6)	150 (39.9)
	Stage IV	31 (8.2)	26 (6.9)
Primary therapy outcome, n (%)	PD	7 (2.3	20 (6.5)
	SD	11 (3.6)	11 (3.6)
	PR	15 (4.9)	28 (9.1)
	CR	125 (40.6)	91 (29.5)
Race, n (%)	Asian	4 (1.1)	8 (2.2)
	Black or African American	14 (3.8)	11 (3)
	White	166 (45.5)	162 (44.4)
Age, n (%)	<=60	113 (29.8)	95 (25.1)
	>60	76 (20.1)	95 (25.1)
Histologic grade, n (%)	G1	0 (0)	1 (0.3)
	G2	22 (6)	23 (6.2)
	G3	160 (43.4)	162 (43.9)
	G4	1 (0.3)	0 (0)
Venous invasion, n (%)	No	23 (21.9)	18 (17.1)
	Yes	29 (27.6)	35 (33.3)
Lymphatic invasion, n (%)	No	28 (18.8)	20 (13.4)
	Yes	49 (32.9)	52 (34.9)
Tumor residual, n (%)	NRD	32 (9.6)	35 (10.4)
	RD	131 (39.1)	137 (40.9)
OS event, n (%)	Alive	79 (20.8)	68 (17.9)
	Dead	110 (29)	122 (32.2)
DSS event, n (%)	Alive	83 (23.4)	71 (20.1)
	Dead	94 (26.6)	106 (29.9)
PFI event, n (%)	Alive	50 (13.2)	52 (13.7)
	Dead	139 (36.7)	138 (36.4)
Age, median (IQR)		58 (50, 66)	60.5 (51, 71)

EOC = epithelial ovarian cancer, FIGO = Federation International of Gynecology and Obstetrics, MMP17 = matrix metalloproteinase 17, TCGA = The Cancer Genome Atlas.

with MMP2 to degrade ECM. However, MMP17's potential involvement and underlying mechanism in EOC is still unknown.

Using RNA sequencing and clinical data of EOC patients retrieved from The Cancer Genome Atlas (TCGA) database, we performed a bioinformatics analysis to determine the role of MMP17 in EOC carcinogenesis and prognosis. MMP-17 was found to be overexpressed in EOC, and its involvement in carcinogenesis was studied. Following that, we conducted a correlation analysis between MMP17 and a number of clinicopathological factors. Finally, we determined MMP-17's diagnostic and prognostic values. This research sheds new light on the mechanisms behind EOC carcinogenesis and identifies MMP17 as a prospective diagnostic and prognostic biomarker in EOC.

2. Materials and Methods

2.1. The data processing and ethics statement

The EOC in the TCGA database (https://portal.gdc.cancer.gov/) provided us with high-throughput sequencing RNA data [fragments per kilobase per million (FPKM) format] and corresponding clinicopathological information. A total of 379 EOC patients were included in the study. For this work, RNA sequencing data were converted from FPKM to TPM formats (transcripts per million reads). The TCGA database confirms that all written informed consents were received prior to data collection because it is open to the public under strict guidelines.

2.2. Differentially expressed genes in EOC

The 379 EOC patients were divided into 2 groups based on their MMP17 expression levels: high and low, according to the median MMP17 expression level. A 2-tailed hypothetical test based on negative binomial generalized linear models was used to identify differentially expressed genes (DEGs) between the 2 groups using the *R* package "DESeq2",[9] with thresholds of a log-fold change >1.0 and an adjusted *P*-value <.05. To exhibit

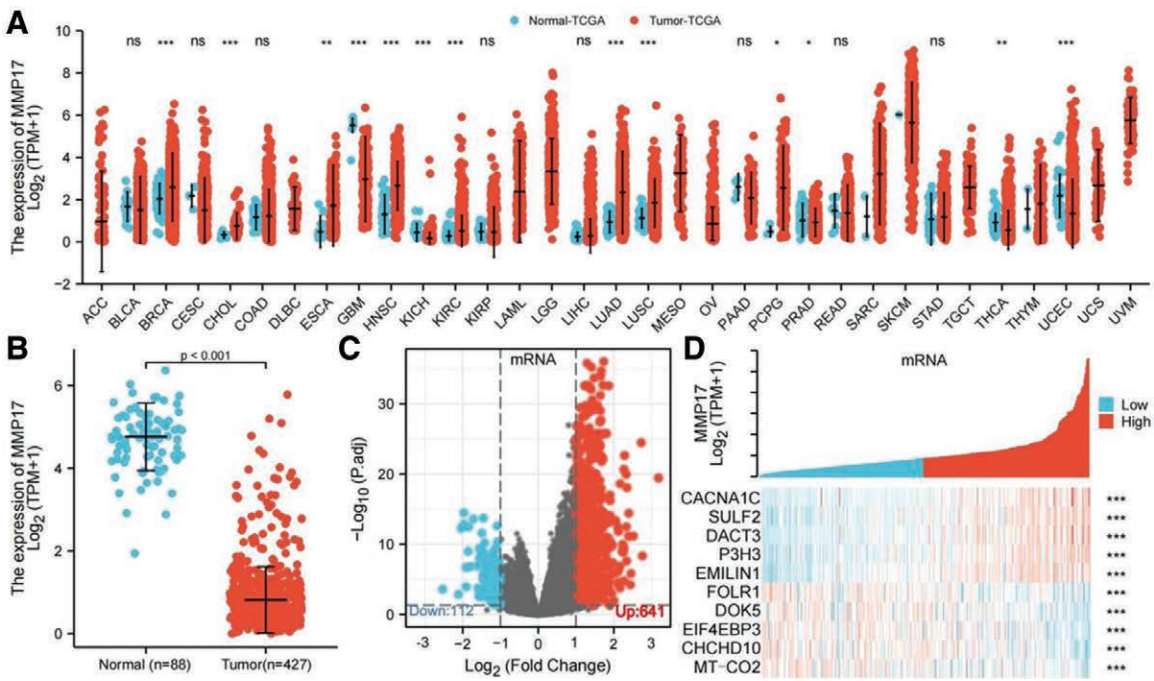

Figure 1. Differential mRNA expression profiles in EOC patients stratified by MMP17 levels. (A) The comparison of MMP17 expression between tumor and pericarcinous tissue in different types of cancers based on TCGA database. ns, $P \geq .05$; *$P < .05$; **$P < .01$; ***$P < .001$. (B) MMP17 expression is higher in EOC than normal tissue. Shown are expression profiles of mRNA in 2 groups; and data are presented by volcano plots (C) and heatmaps (D). EOC = epithelial ovarian cancer, MMP17 = matrix metalloproteinase 17, TCGA = The Cancer Genome Atlas.

the results as heatmaps and volcano plots, the *R* package "ggplot2, edition 3.3.3" was used.

2.3. Functional annotation of MMP17 associated differentially expressed genes in EOC

The DEGs were then processed on the Metascape database (https://metascape.org/) and online tool[10] for functional annotation. Analysis thresholds were established at minimum counts >3, enrichment factors >1.5, and a *P*-value <.01. The Gene Set Enrichment Analysis (GSEA)[11] of the DEGs in the 2 groups was also performed using the *R* package "clusterProfiler".[12] As reference gene sets in GSEA, C2: curated gene sets from MSigDB collections were chosen. There were 626 clusters found in total, with clusters having a false discovery rate (FDR) <0.25 and a *P*-value <.05 being considered significant. Protein-protein interaction networks were investigated using the STRING database (http://string-db.org)[13] and displayed using the Cytoscape software (version 3.7.2).[14] The mutation of MMP17 was checked by the database (https://www.cbioportal.org/).[15,16]

2.4. Association of MMP17 and immune cell infiltration in EOC

Infiltration enrichment of 24 common immune cells[17] was shown using the single sample GSEA technique from the *R* package "GSVA version 1.34.0".[18] The relationship between MMP17 expression and immune cell infiltration was assessed using Spearman's analysis, and immune cell infiltration levels were compared using the Wilcoxon rank sum test for high- and low-MMP-17 expression groups.

2.5. Clinical significance of MMP17 expression in EOC

The predictive potential of MMP17 for EOC diagnosis was tested by comparing MMP17 expression in EOC and normal tissues using receiver operating characteristic (ROC)

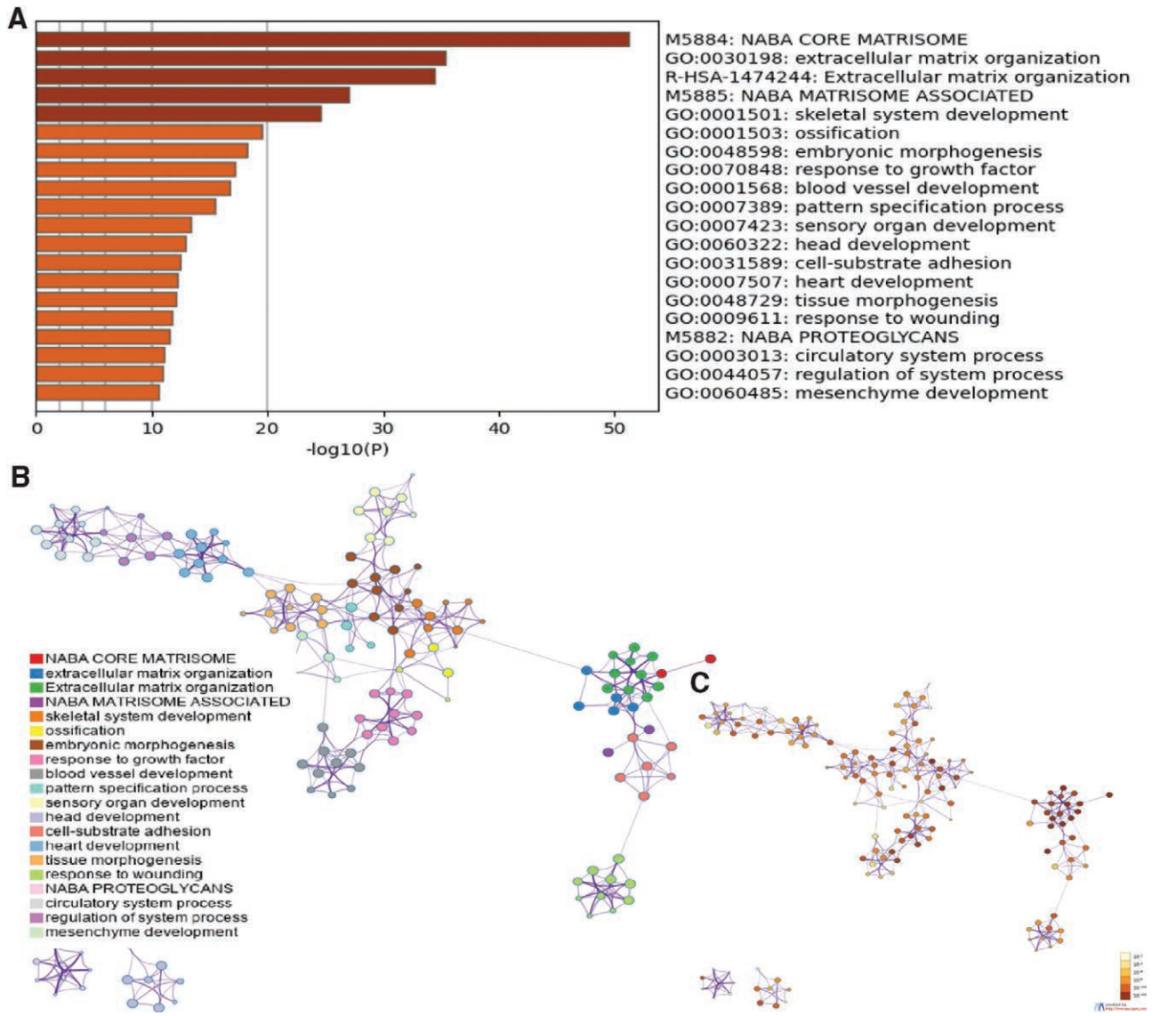

Figure 2. Functional annotation of DEGs in EOC with distinct MMP17 levels. According to the Metascape database, 753 differentially expressed mRNAs between high- and low-MMP17 expression groups were used for functional annotation. All statistically enriched terms were identified and then hierarchically clustered into a tree (A) based on the threshold of kappa score as 0.3. Representative terms from the cluster were converted into a network layout (B). The size of a node is proportional to the number of input genes that fall into that term, and the respective color represents its cluster identity. Terms with a similarity score > 0.3 are linked by an edge (the thickness of the edge represents the similarity score). The same enrichment network presents nodes colored by the *P* value (C). EOC = epithelial ovarian cancer, DEGs = differentially expressed genes, MMP17 = matrix metalloproteinase 17.

analysis. The EOC data were extracted from TCGA, as well as the corresponding normal tissue data from GTEx. The Toil process[19] was used to convert and normalize RNA-sequencing data in Fragments Per Kilobase Per Million format (FPKM) into transcripts per million (PTM) reads, which were then log2 transformed for further analysis. The analysis was carried out using the *R* package "pROCversion1.17.0.1" and the visualization was carried out using "ggplot2 version 3.3.3."

A published study[20] provided information on EOC patients's clinical outcomes, including overall survival, progression-free interval, and disease-specific survival. For the prognosis analysis, Kaplan–Meier (K–M) analysis, univariate, and multivariate Cox regression analyses were used. The nomograms and calibration plots were created using the *R* packages "rms version 6.2-0" and "survival version3.2-10". *R* software (version 3.6.3) was used to conduct all of the aforementioned statistical studies, with *P*-values <.05 deemed significant.

3. Results

3.1. Clinical characteristics

TCGA provided the clinical histories of 379 patients, including age, race, Federation International of Gynecology and Obstetrics (FIGO) stage, primary therapeutic outcome, histologic grade, venous invasion, lymphatic invasion, and tumor residual, as well as overall survival (OS), disease-specific survival (DSS), and progression-free interval (PFI) events. The details were presented in Table 1.

3.2. Expression profiles of MMP17 in different cancers and related differentially expressed genes in EOC

Using the TCGA database, MMP17 was found to be significantly overexpressed in 13 of the 33 cancer types investigated, as shown in Fig. 1A. MMP17 expression was much higher in EOC patients than in pericarcinous tissues ($P < .001$, Fig. 1B).

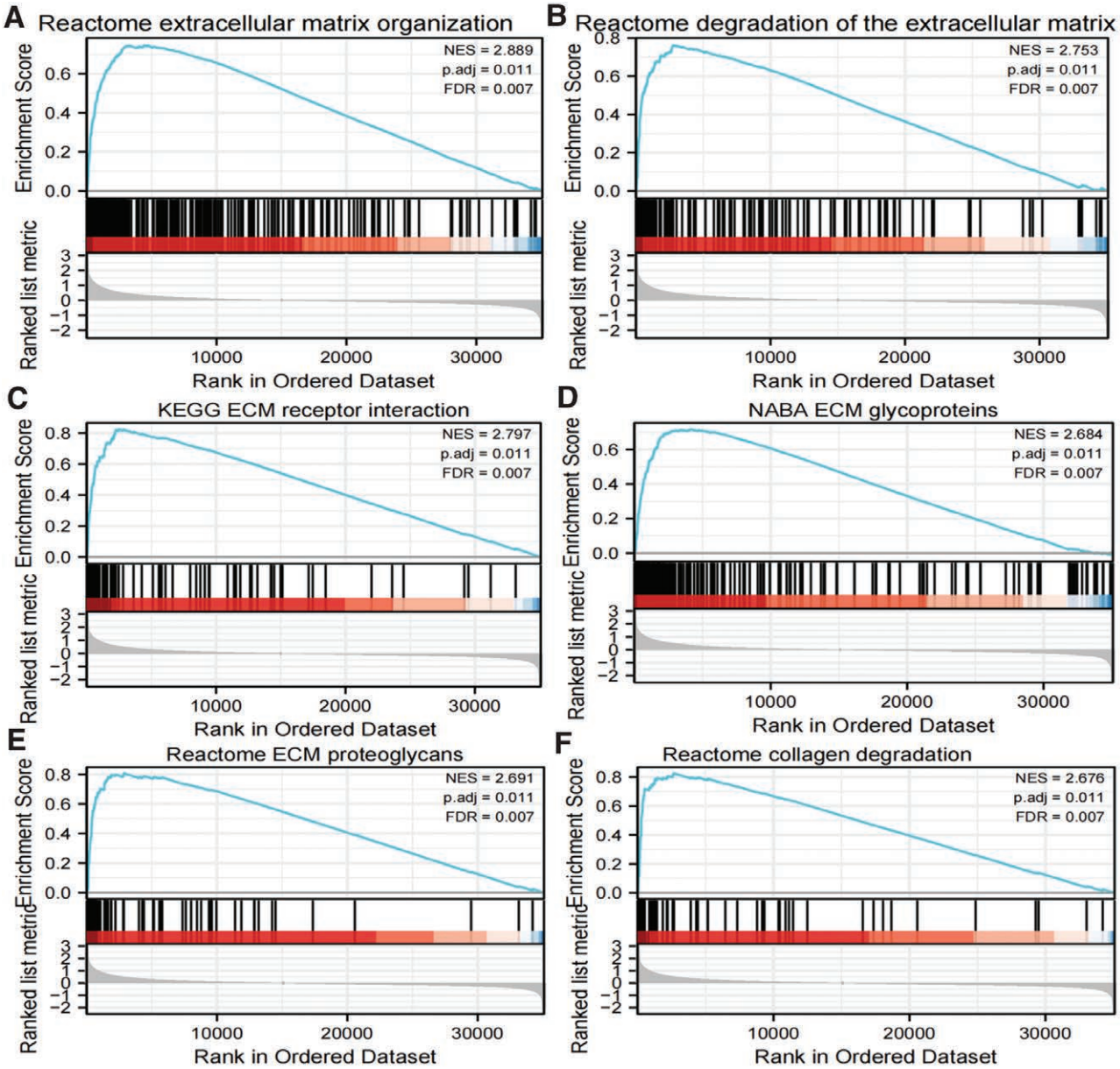

Figure 3. Representative Gene Set Enrichment Analysis of differentially expressed mRNAs between high- and low-MMP17 expression groups. MMP17 = matrix metalloproteinase 17.

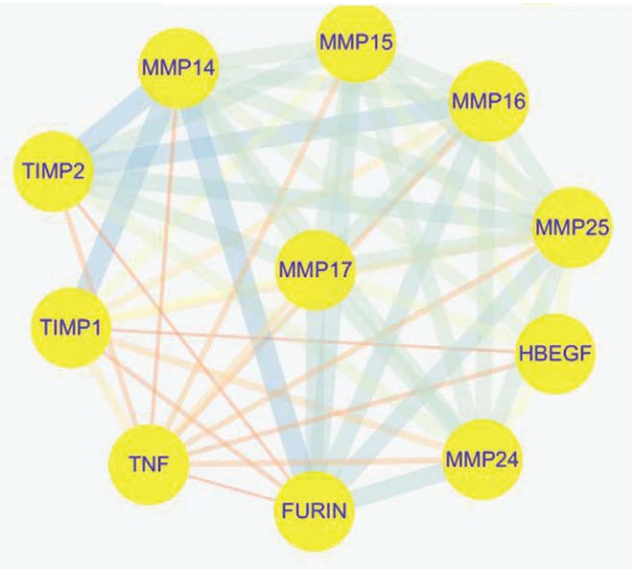

Figure 4. PPI network for MMP17, the most frequent 10 neighbor genes. MMP17 = matrix metalloproteinase 17, PPI = protein-protein interaction networks.

Based on median MMP17 expression in EOC, 379 OC patients were split into 2 groups: high- and low-MMP17 expression groups. Following that, we looked at the mRNA expression of 2 separate groups. Volcano plots (Fig. 1C) indicated 753 mRNAs (641 upregulated and 112 downregulated) that were recognized as DEGs (absolute value of fold change > 1.0, P<.05). In addition, a heatmap was employed to depict representative DEGs. The top 5 positive related genes were CACNA1C, SULF2, DACT3, P3H3, and EMILIN1, while the negative associated genes were FOLR1, DOK5, EIF4EBP3, CHCHD10, and MT-CO2 (Fig. 1D).

3.3. Functional annotation of MMP17 associated differentially expressed genes in EOC

Several EOC-related pathways were enhanced, as shown in Figure 2A–C, including extracellular matrix organization (GO:0030198), skeletal system development (GO:0001501), blood vessel development (GO:0001568), and cell substrate adhesion (GO:0001568).Furthermore, MMP17-associated DEGs were significantly enriched in cell ECM clusters (Fig. 3A–F), including extracellular matrix organization (normalized enrichment score [NES] = 2.889, adjusted P = .011), ECM receptor interaction (NES = 2.797, adjusted P = .011), ECM degradation (NES = 2.752, adjusted P = .011), EMC proteoglycans (NES = 2.691, adjusted P = .011),EMC glycoproteins (NES = 2.683, adjusted P = .011) and collagen degradation (NES = 2.675, adjusted P = .011).We also constructed a protein-protein interaction networks to illustrate that MMP17 served as the hub gene related to another ten genes, which included TNF, TIMP1, MMP14, MMP15, MMP16, and FURIN, etc. (Fig. 4).

3.4. Mutation of MMP17 in EOC

The database supplied 5 datasets for further analysis, which were enrolled by us for the query of mutations for MMP17 in the EOC. The mutation rate in this study was 1.5% (Fig. 5A). Only 1 sample ID, TCGA-23-2643-01, from ovarian serous cystadenocarcinoma (TCGA, PanCancer Atlas) had protein change at D317E, and the mutation type was missense (Fig. 5B).

3.5. Association of MMP17 and immune cell infiltration in EOC

The ssGSEA method was used to determine the infiltration of 24 immune cell types in EOC, and then Spearman analysis was used to evaluate the relationship between MMP17 and immune cell infiltration. Tem (R = 0.357, P < .001), macrophages (R = 0.333, P < .001), and NK cells (R = 0.389, P < .001) were all strongly linked with MMP17 expression, as shown in Figure 6A. Th17 cells (R = −0.195, P < .001) and NK CD56bright cells (R = −0.107, P = .037) were found to have a negative relationship with MMP17. The full details of immune cell correlation were illustrated by (Table S1, Supplementary Digital Content, http://links.lww.com/MD/H127).We assessed at the levels of infiltration of the most important immune cells (Fig. 6B,C) in different MMP17 groups, and the results were consistent with those in Figure 6A.

3.6. Predictive value of MMP17 for EOC diagnosis and prognosis

The evaluation of MMP17 on discriminating EOC diagnosis was demonstrated using a ROC curve. MMP17 has a high

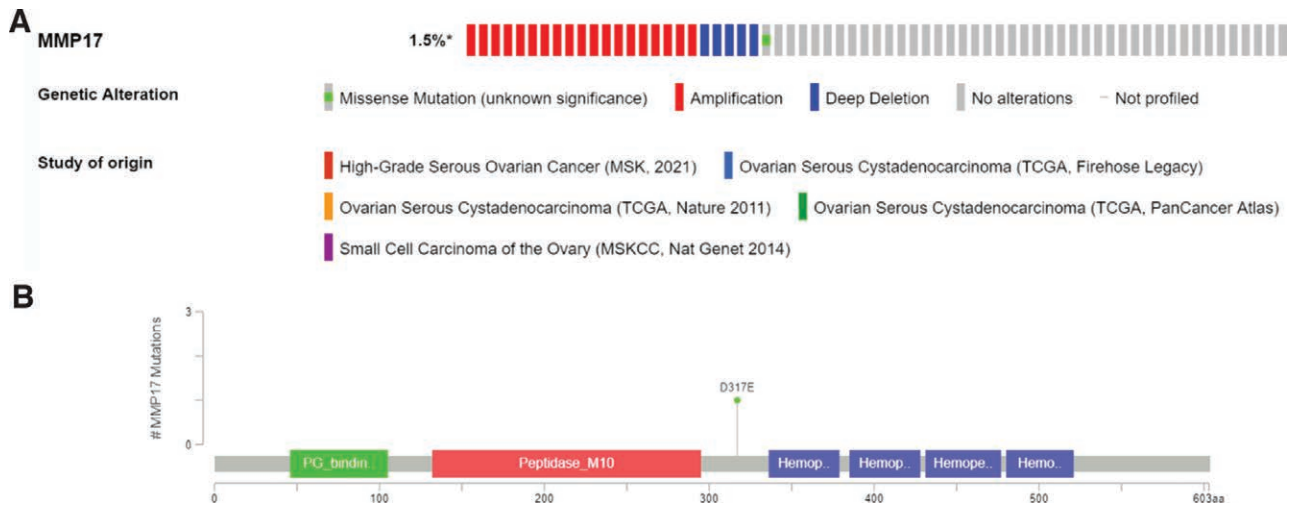

Figure 5. Mutation of MMP17 in EOC (A) MMP17 gene expression and mutation analysis in EOC. (B) The graphical view showed the Pfam protein domains and the positions of specific mutations. EOC = epithelial ovarian cancer, MMP17 = matrix metalloproteinase 17.

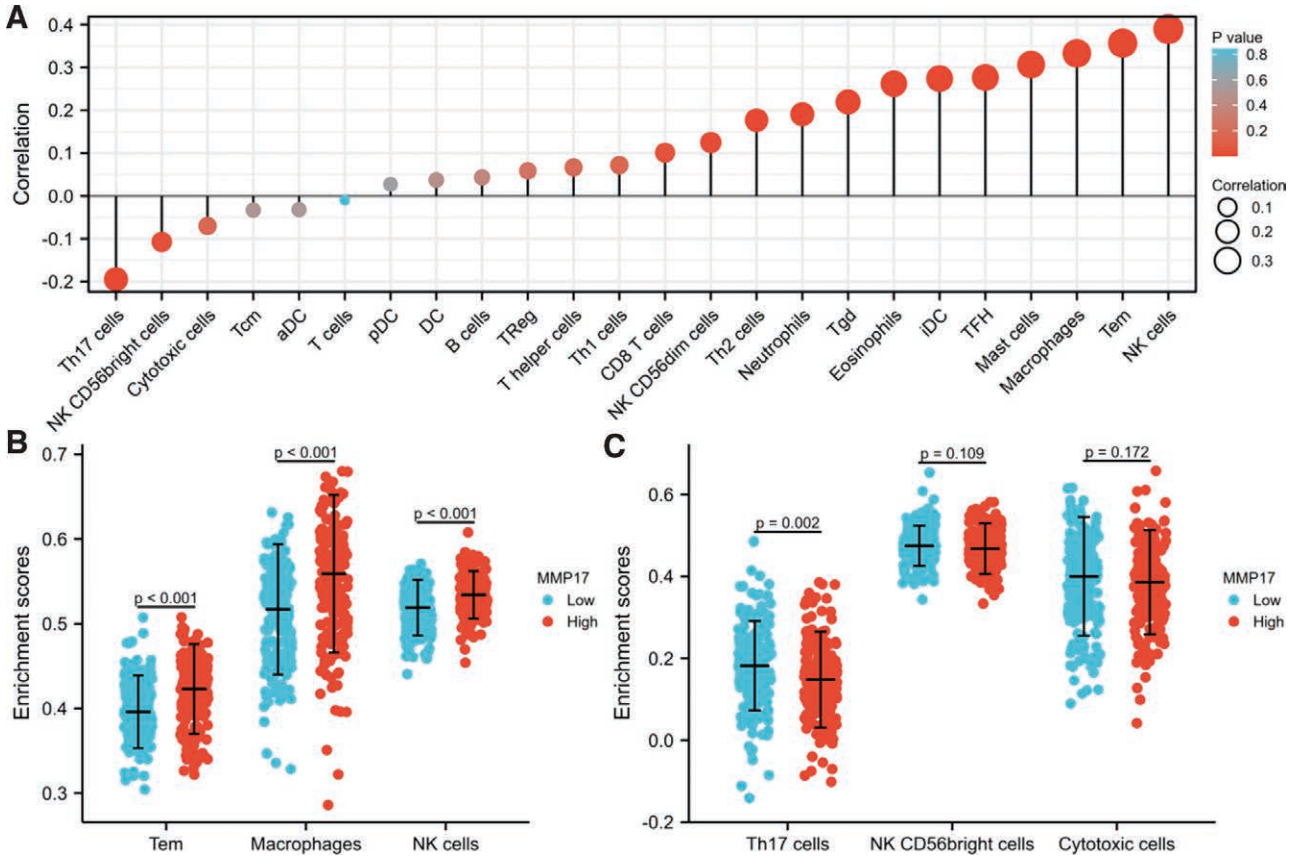

Figure 6. Correlation of immune cell infiltration and MMP17 expression in EOC patients. (A) Relationships among infiltration levels of 24 immune cell types and MMP17 expression profiles by Spearman analysis. Shown is the comparison of infiltration levels of most correlated immune cells, including Tem, macrophages and NK cells (B), Th17 cells, NK CD56bright cells and Cytotoxic cells (C) between high- and low-MMP17 expression groups. aDC [activated DC]; B cells; CD8 T cells; Cytotoxic cells; DC; Eosinophils; iDC [immature DC]; Macrophages; Mast cells; Neutrophils; NK CD56bright cells; NK CD56dim cells; NK cells; pDC [Plasmacytoid DC]; T cells; T helper cells; Tcm [T central memory]; Tem [T effector memory]; Tfh [T follicular helper]; Tgd [T gamma delta]; Th1 cells; Th17 cells; Th2 cells; Treg. EOC = epithelial ovarian cancer, MMP17 = matrix metalloproteinase 17.

sensitivity and specificity for EOC diagnosis, with an area under the curve (AUC) of 0.988. (Fig. 7A). Following that, K–M analyses were used to confirm MMP17's prediction of clinical outcomes. Overall survival (HR: 1.69, $P < .001$), progression-free interval (HR: 1.42, $P = .004$), and disease-specific survival (HR: 1.72, $P < .001$) for high-MMP17 expression groups were all substantially worse than for low-MMP17 groups, as illustrated in Figure 7B–D.

We also ran a multivariate Cox regression analysis to see if MMP17 had any predictive value for clinical outcomes. In multivariate Cox regression, MMP17 expression was found to be an independent risk factor for overall survival (HR: 1.488, $P < .001$), progression-free interval (HR: 1.347, $P < .01$), and disease-specific survival (HR: 1.548, $P < .01$); however, FIGO stage, age, and race showed no prognostic advantages for clinical outcomes, as shown in Table 2.

Each multivariate Cox regression analytic statistically significant prognostic factors were then utilized to design a prognostic nomogram. A calibration curve was constructed to assess the nomogram's effectiveness. FIGO stage, age, and race, as well as MMP17 were included into the nomogram to predict OS [(C-index of 0.694) (Fig. 8A)], DSS [(C-index of 0.701) (Fig. 8C)], and PFI [(C-index of 0.653) (Fig. 8E)].The calibration curves for the 3 nomograms for 1-, 3-, and 5-year clinical outcomes all showed promising results, with the exception of the 3- and 5-year predictions for DSS and forecast PFI, which were lacking in data (Fig. 8B, D, and F)

3.7. Prognostic performance of MMP17 in EOC subgroups

The next step was to see if MMP17 had any prognostic value for clinical outcomes in a variety of clinicopathological categories. In certain subgroups, we ran Cox regression analysis, and the results were shown as forest plots (Fig. 9). In patients with tumor (HR = 1.76, $P = .000$), FIGO stage III–IV (HR = 1.72, $P = .000$), histology G3-4 (HR = 1.77, $P = .000$), and tumor residual (HR = 1.60, $P = .001$), MMP17 was a significant risk factor for overall survival (Fig. 9A). Figure 9B shows similar findings for disease-specific survival and progression-free intervals (Fig. 9C). MMP17 was also found to be an independent risk factor for all ages and anatomic subdivisions.

In addition, we reported K–M analyses for clinical outcomes (overall survival, progression-free interval, and disease-specific survival) in 4 representative subgroups: age under 60, tumor status, and anatomic neoplasm subdivision (Fig. 10A–L). All of these findings showed that the low-MMP17 expression group had considerably superior clinical outcomes.

4. Discussion

In our study, we found that MMP17 was significantly elevated in gynecologic cancers, such as UCEC and CESC. Moreover, MMP17 was also upregulated in tumors, such as THCA, PAAD, PRAD, READ, SKCM, and other systems. As a result, MMP17 might be an important hub gene in tumorigenesis. Further, by examining information from the TCGA-OV, MMP17

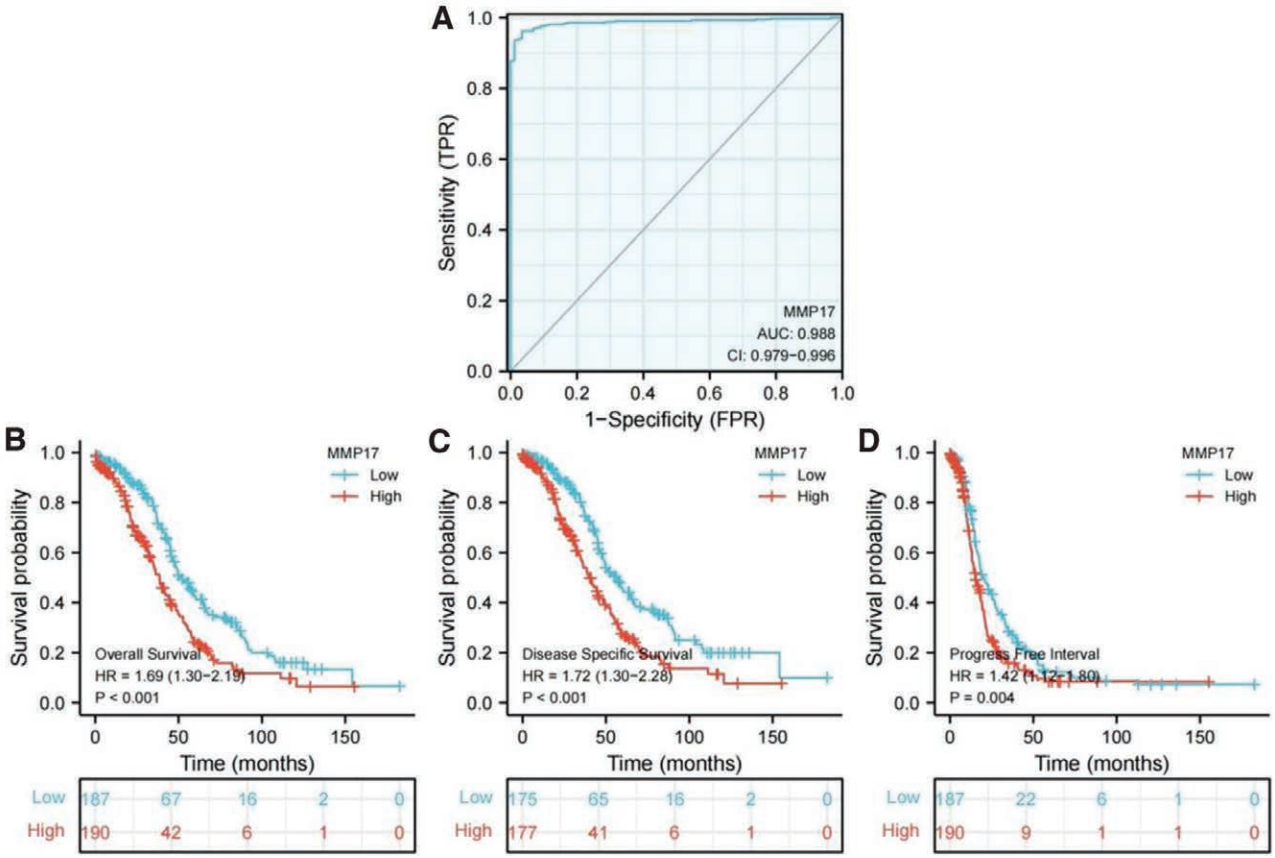

Figure 7. Predictive value of MMP17 expression for diagnosis and clinical outcomes in EOC patients. (A) ROC curve analysis evaluating the performance of MMP17 for EOC diagnosis. Shown are the Kaplan–Meier analyses comparing overall survival (B), progression-free interval (C), and disease-specific survival (D) between high- and low-MMP17 expression groups. EOC = epithelial ovarian cancer, MMP17 = matrix metalloproteinase 17, ROC = receiver operating characteristic.

expression was shown to be significantly higher in EOC than normal tissues. DEGs linked to elevated MMP17 expression were discovered to be localized in cell ECM-related pathways and bioprocesses, indicating that MMP17 has a role in ECM mechanism during EOC carcinogenesis. The ECM protease, MMP17, is strongly associated with the degradation of membrane of cell.[6] MMP17 proteolytic activity determines the phenotypic of vascular smooth muscle cells in the arterial artery wall, and animals lacking it are predisposed to thoracic aortic aneurysm.[21] MMP17 affects intestinal epithelial reprogramming after damage.[22] These founding are consistent with the GO and GSEA enrichment analysis of MMP17 in EOC patients in our study.

In EOC patients, our study found that the high expression of MMP17 is negative correlated with OS, PFI, and DSS. Particularly, those EOC patients with advanced stages, high histologic grades, and residual tumor had worse outcome, suggesting that MMP17 may play an important role in tumor progression. Agarwal et al[23] and Rasool et al[24] also reported that MMPs could promote the cancer invasion and metastasis. Meanwhile, a strong link between MMP17 expression and age, histologic grade, and clinical stage was discovered. The above clinical characteristics are directly associated to ovarian cancer patient's prognosis, and they also happen to be obstacles in the therapeutic treatment of ovarian cancer patients.[25,26] The MMP17 maybe a new biomarker to resolve this dilemma according to our finding.

Table 2

Cox regression analysis for clinical outcomes in EOC patients.

	HR for overall survival (95% CI)		HR for progression-free interval (95% CI)		HR for disease-specific survival (95% CI)	
Characteristics	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Age (>60 vs ≤60 yr)	1.355*	1.316	1.255	NA	1.255	NA
FIGO stage (I & II vs III & IV)	2.115	2.602	1.573	1.558	2.276	2.474
Primary therapy outcome (PD & D vs PR & CR)	0.301***	0.317***	0.457***	0.507***	0.294***	0.33***
MMP17 (high vs low)	1.639***	1.488***	1.39**	1.347**	1.693***	1.548**
Race (White vs Black or African American and Asian)	0.637	0.61	0.843	NA	0.592*	0.601

CI = confidence interval, EOC = epithelial ovarian cancer, FIGO = Federation International of Gynecology and Obstetrics, HR = hazard ratio, MMP17 = matrix metalloproteinase 17.

*$P < .05$.

**$P < .01$.

***$P < .001$.

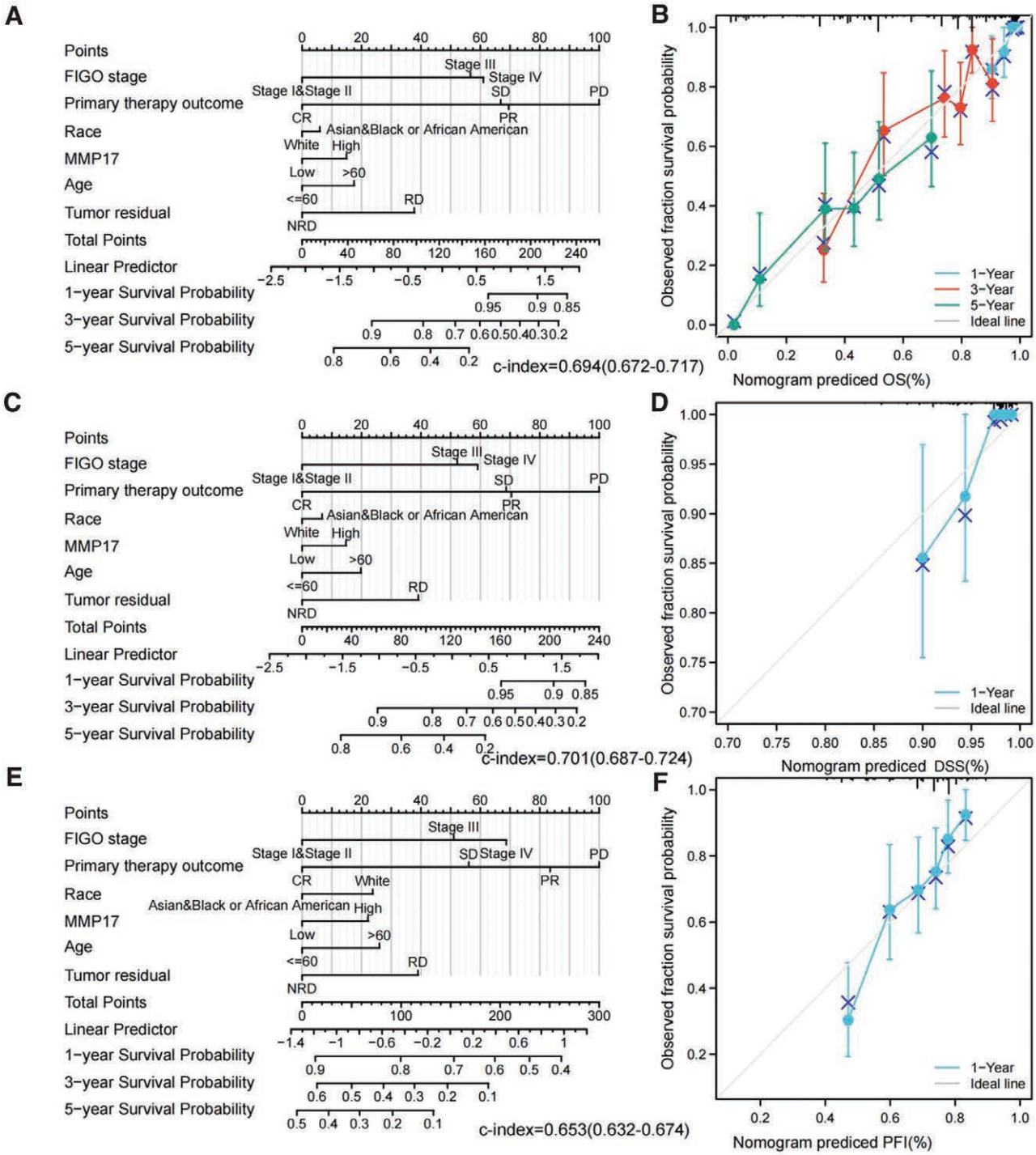

Figure 8. Construction and validation of nomograms based on MMP17 expression. Shown are the nomograms constructed to establish MMP17 expression-based risk scoring models for 1-, 3-, and 5-year overall survival (A), disease-specific survival (C), and progression-free interval (E). Calibration plots validating the efficiency of nomograms for overall survival (B), disease-specific survival (D), and progression-free interval (F). DSS = disease-specific survival, OS = overall survival, MMP17 = matrix metalloproteinase 17, PFI = progression-free interval.

Further, we attempted to describe the potential functions and mechanisms involving MMP17 in EOC. The initial barrier in the process of tumor metastasis was the ECM and substrate, and its degradation was the critical link in the tumor invasion and metastasis.[27,28] Extracellular matrix organization, blood vessel development, and skeletal system development were all linked to MMP17 expression. ECM protein controls transmembrane protein phosphorylation status, which could control cell behavior.[29] MMPs degrading activities in ECM cause changes in its structure and expression of its cellular surface receptors, resulting in the occurrence, development, invasion, and metastasis of malignant tumors.[6,7,30] These bioprocesses are in accordance with our GSEA results, which form the pathways of ECM degradation, ECM receptor interaction, EMC glycoproteins, and ECM organization. TIMP1 (Tissue inhibitors of matrix metalloproteinases), which is strongly connected with the size of primary ovarian cancers,[31] acted as the

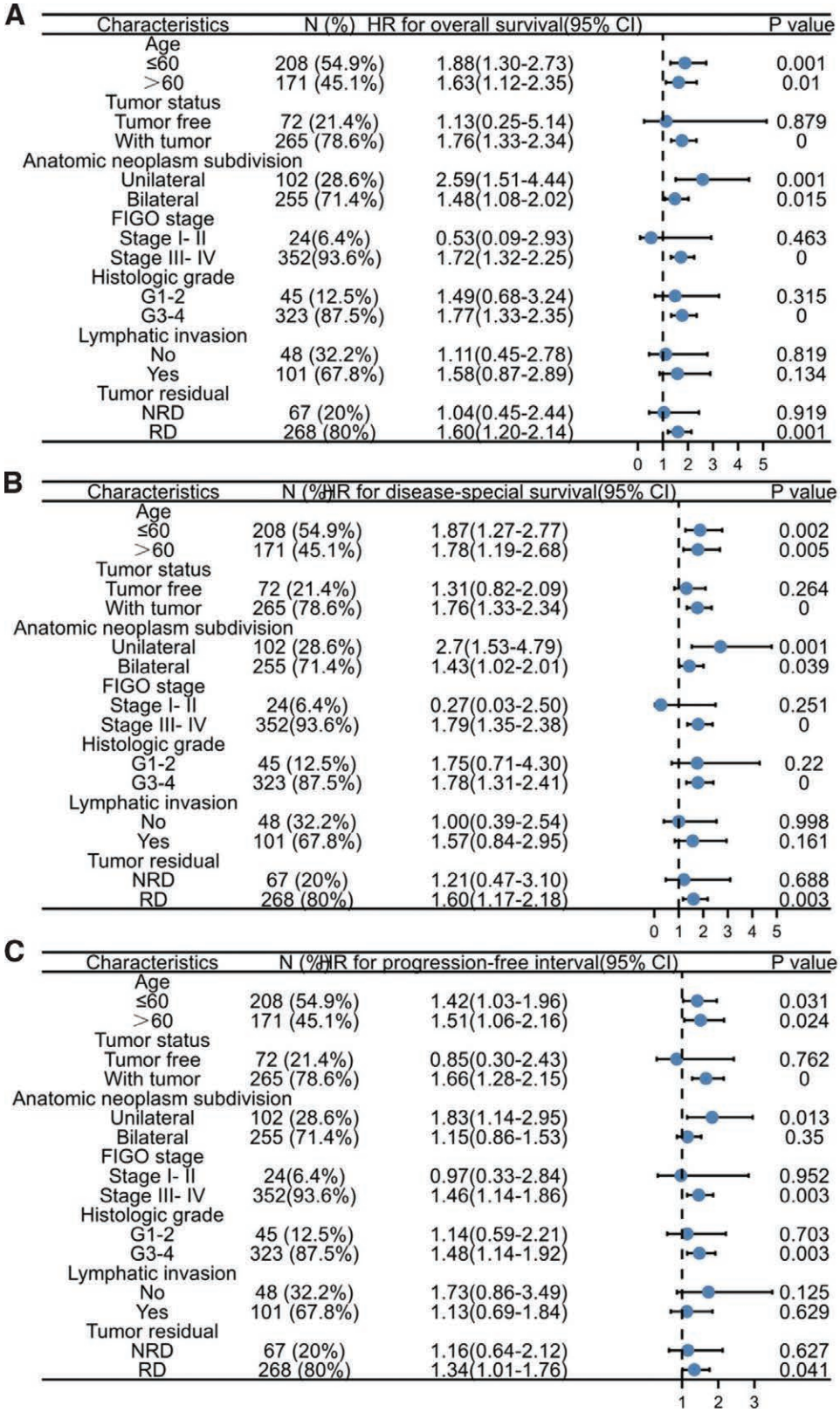

Figure 9. Prognostic performance of MMP17 on clinical outcomes in different EOC patient subgroups. Patients were divided into different subgroups according to age, tumor status, anatomic neoplasm subdivision, FIGO stage, histologic grade, lymphatic invasion, and tumor residual. For each subgroup, the prognostic performance of MMP17 on overall survival (A), disease-specific survival (B), and progression-free interval (C) were evaluated by Cox regression, and the results are presented as HR. The bar represents the 95% confidence interval of HR, and the diamond's size represents the significance of MMP17s performance. EOC = epithelial ovarian cancer, HR = hazard ratio, MMP17 = matrix metalloproteinase 17.

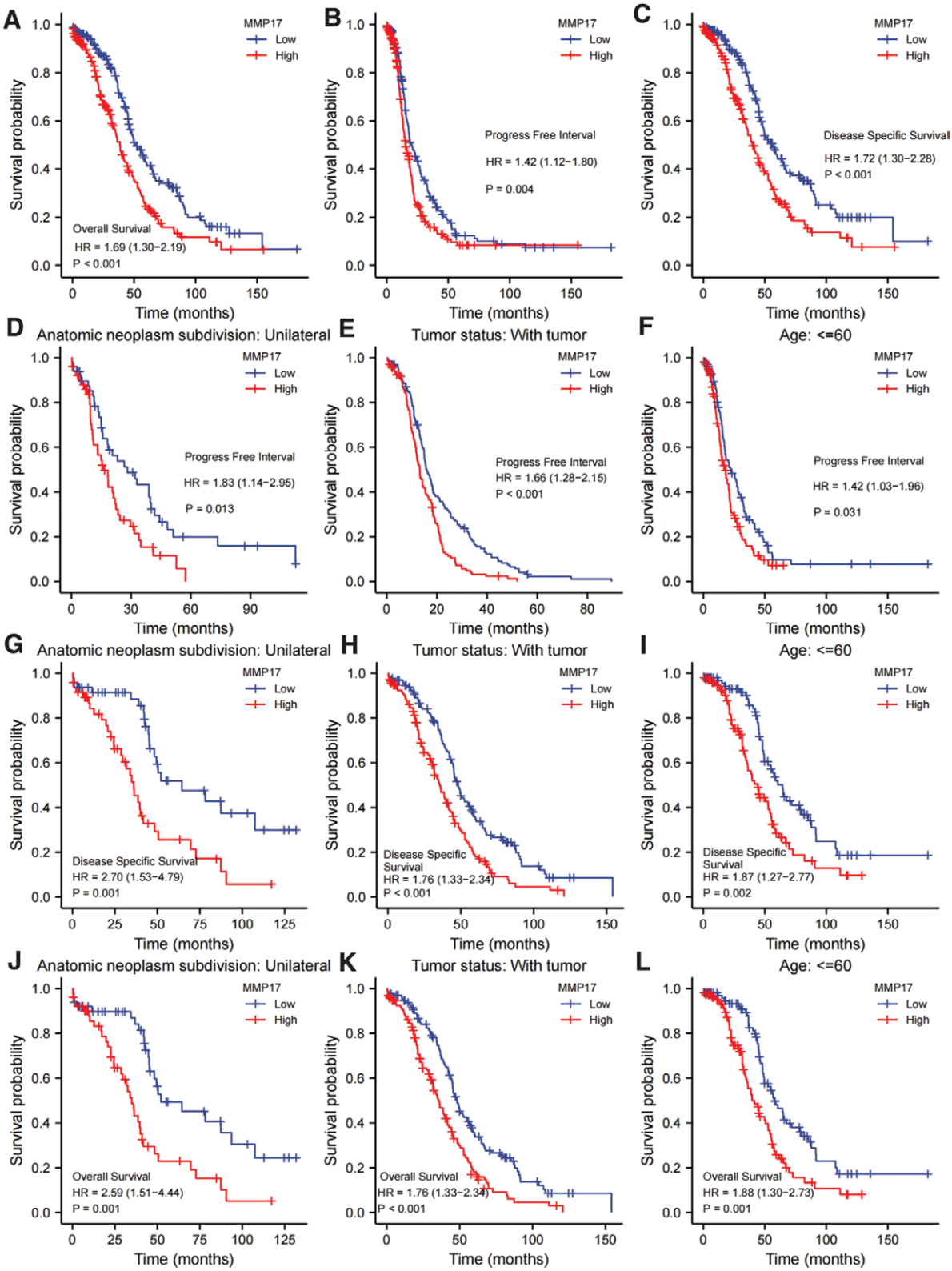

Figure 10. Distinct clinical outcomes based on MMP17 expression in EOC patient subgroups. Kaplan–Meier analysis showing the comparison of overall survival (A), progression-free interval (B), and disease-specific survival (C) between high- and low-MMP17 expression groups. The subgroups included age below 60 years (F, I, L), tumor status (E, H, K), and anatomic neoplasm subdivision (D, G, J). EOC = epithelial ovarian cancer, MMP17 = matrix metalloproteinase 17.

hub gene for MMP17. Rauvala et al[32] stated that increased TIMP1 level associated with the progressive ovarian cancer. Normally, MMPs's protease activity can be inhibited by TIMPs by forming stable and irreversible noncovalent bonds with active MMPs.[6] The imbalance of MMPs and TIMPs is linked to ovarian cancer invasion and metastasis, despite the fact that the underlying mechanisms are yet unknown. Membrane-type specific MMP17 could trigger MMP2 to improve type IV collagen and gelatin cleavage and denaturation,[6] this may enhance the metastasis of EOC. MMP17

operates as a major ECM regulator in EOC, according to the results presented above.

In addition, we discovered a link between MMP17 expression and immune cell infiltration. MMP17 expression was associated with cytotoxic cells, Th17 cells, and NK CD56bright cells in a negative way. The findings are consistent with prior research on immune infiltrates in ovarian cancer.[33–35] Th17 cells activate effector CD8(+) T cells and induce anticancer immune responses by recruiting immune cells into tumors.[36] Winkler et al[33] stated that Th17 cells could promote tumor progression by increasing inflammatory angiogenesis. Antitumor immunity can be initiated by cytotoxic CD8 + T cells, and NK CD56bright cells have been shown to have antitumor responses after being primed with IL-15.[37] MMP17 expression is consistent with immune macrophages and DCs, which play a role in cancer progression and contribute to intrinsic immunity.[38,39] Macrophage infiltration is linked to a poor prognosis in solid tumors and chemotherapy resistance in most cancers.[37,40,41] As a result, overexpressed MMP17 may wreak havoc on tumor immunity, aid ovarian cancer cells in evading elimination, and hasten carcinogenesis.

In a focusing on MMPs family study, reporting MMP17 was not associated with overall survival in ovarian cancer patient,[42]This dramatic result may be related the database they took.[43]

In conclusion, MMP17's clinical relevance in EOC is undeniable. Firstly, in our study, the AUC of the ROC curve for MMP17 discrimination of EOC diagnosis was 0.988, indicating that MMP17 was a reliable biomarker for EOC diagnosis. Secondly, patients with increased MMP17 levels had a significantly reduced rate of OS, PFI, and DSS. Lastly, MMP17's predictive value appeared to be stronger in patients with certain clinical variables, such as advanced stage, high histologic grade, and residual tumor. MMP17 has a crucial role in EOC proliferation, metastasis, and treatment strategy, as shown by the preceding findings. MMP17's ability to predict poor survival in EOC raised the potential that it may be used as a common prognostic biomarker.

Despite the fact that we uncovered a plausible mechanism for MMP17 activity in EOC carcinogenesis and its predictive utility in clinical outcomes, our study had major shortcomings. First, we were unable to assess a specific role for MMP17 in EOC treatment due to a lack of knowledge about treatments and their outcomes. Second, we primarily employed the TCGA database's RNA sequencing data; therefore, we couldn't provide information on relative protein levels or MMP17's downstream pathways. As a result, more in vivo and in vitro research focusing on the direct mechanism of MMP17 activity in EOC will be needed.

5. Conclusions

Increased MMP17 expression in EOC may contribute to carcinogenesis by degrading ECM and provide diagnostic and prognostic value for clinical outcomes.

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