



# MMP11 and MMP17 are potential biomarkers for uterine corpus endometrial carcinoma prognosis

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## Abstract

**Background** Matrix metalloproteinases (MMP) are important proteases that degrade the extracellular matrix (ECM) and thus essentially mediate tumor vascularization, metastasis, and invasion. However, their potential roles in uterine corpus endometrial carcinoma (UCEC) are not fully understood.

**Patients and methods** The expression, prognostic value, and correlation of UCEC patients with MMP were investigated using data from The Cancer Genome Atlas (TCGA) and other databases. Furthermore, differentially expressed genes (DEGs) were identified and their biological functions and correlations with infiltrating immune cells were analyzed.

**Results** A total of 22 MMPs were found to be abnormally expressed in UCEC tumor tissues, and high expression of MMP11 and MMP17 were associated with a better UCEC prognosis. MMP11 and MMP17 were observed to be significantly enriched in tumor tissue ECM and were associated with pathways involving degradation, glycolytic metabolism, and PI3K-Akt signaling. Infiltration of natural killer (NK), mast, and NK CD56bright cells was enhanced in tumor tissues with high MMP11 and MMP17 expression.

**Conclusion** MMP11 and MMP17 may affect UCEC prognosis by influencing immune cell infiltration and may be potential UCEC biomarkers.

**Keywords** MMPs · Prognosis · Uterine corpus endometrial carcinoma · Immune cell infiltration

## Introduction

Uterine corpus endometrial carcinoma (UCEC) is a common gynecological malignancy, with increasing incidence and mortality rates. The cause of its development has not been clarified, and treatment primarily involves surgery and radiotherapy [1, 2].

Matrix metalloproteinases (MMPs) are a metal ion-dependent multigene family of endopeptidases, first identified in 1962 by Gross and Lapiere in the tails of tadpoles. There are 24 well-defined MMPs grouped into six major classes, as shown in Table 1 [3, 4]. Most MMPs are secreted into the extracellular environment as inactive zymogens

that regulate the activities of other proteases, growth factors, cytokines, and cell surface ligands and receptors. They are essential for normal physio-pathological processes [5]. MMPs can degrade extracellular matrix (ECM) components (such as fibronectin), break down cell surface molecules (such as E-cadherin), disrupt cell–cell adhesion, and promote tumor cell migration and invasion [6, 7]. In addition, MMPs have been shown to initiate or terminate immune processes within tumor tissues by modifying both soluble and membrane-bound proteins in the extracellular environment [8, 9].

Recently, there has been increased interest in the role of MMPs in tumor immune responses, especially in relation to immunotherapy; however, their role in the prognosis, development, and immunotherapy of UCEC still needs to be determined. Therefore, this investigation used multiple comprehensive analyses to investigate the expression of MMPs and their potential roles in UCEC.

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**Table 1** The MMP subfamily and its members

Subfamily	Members
Collagenases	MMP-1, -8, -13
Gelatinases	MMP-2, -9
Stromelysins	MMP-3, -10
Matrilysins	MMP-7, -26
Furin-containing MMPs	MMP-11, -14, -15, -16, -17, -21, -23, -24, -25, -28
Other MMPs	MMP-12, -19, -20, -22, -27

## Methods

### Analysis of differences in MMP expression

RNA-sequencing (RNA-seq) data in the transcripts per million (TPM) read format were acquired from The Cancer Genome Atlas (TCGA). Toil applications were imported from TCGA (<https://portal.gdc.cancer.gov/>) and UCSC XENA (<https://xenabrowser.net/datapages/>) [10]. In total, 589 cases with clinical information from TCGA and 282 cases from UCSC XENA were collected after discarding those without RNA-seq data and with overall survival (OS) of fewer than 30 days. MMP expression levels were compared between tumor and control samples using the Wilcoxon rank sum test. The effectiveness of MMP expression for discriminating between UCEC and healthy samples in TCGA was assessed by receiver operating characteristic (ROC) curves using the pROC package and was validated using the GEO dataset [11].

### Survival curve assessments

Kaplan–Meier survival curves were plotted using the survminer package in R (version 0.4.4; <https://CRAN.R-project.org/package=survminer>) to assess the ability of MMPs to predict patient survival. Log-rank tests were used to assess differences in survival between the low and high MMP-expression groups.

### Association of MMPs with clinicopathological parameters

Pearson  $\chi^2$  tests were used to assess the associations between MMP expression (high or low based on the median) and clinicopathological variables. The Fisher exact test was applied when needed. The Kruskal–Wallis

rank sum test was used to assess MMP expression in association with different clinicopathological features.

### Analysis of differentially expressed genes (DEGs) between low and high MMP expression subgroups

Tumor specimens were classified into low and high MMP-expression subgroups based on the expression median. DEGs associated with low and high MMP11 and MMP17 expression were identified. DEGs were identified from HTSeq-Counts using DESeq2 software and the thresholds of  $|\log_2$  fold change (logFC)| > 1 and adjusted  $P$  value < 0.05 [12].

### Functional annotation and pathway enrichment analyses of DEGs

The R package ClusterProfiler (3.14.3) was utilized for Gene Ontology (GO) classification, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment, and Gene Set Enrichment Analysis (GSEA) of DEGs in low and high MMP-expression groups [13]. MMP11 and MMP17 expression were used as phenotype labels. The pathway enrichment criterion was adjusted  $P < 0.05$ .

### Immune infiltration analysis

Tumor infiltration of 24 immune cell types was evaluated using the single-sample GSEA (ssGSEA) method [14], and the relative enrichment scores of each specimen were determined. The associations between MMP expression and the infiltration of each immune cell type were elucidated by Spearman correlation analysis. Immune cell infiltration in the low and high MMP-expression groups was compared using Wilcoxon rank sum tests.

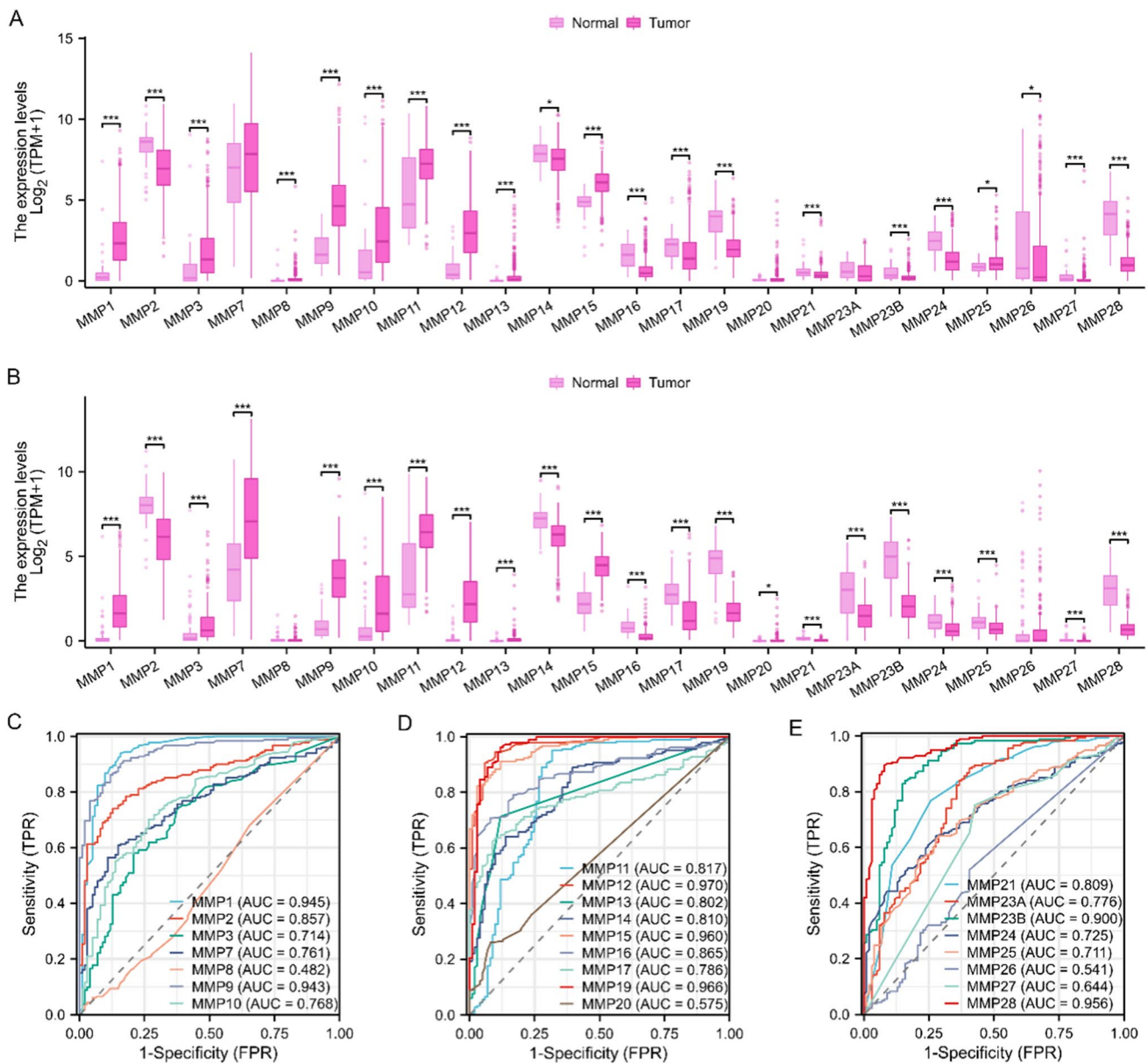
### Statistical measurements

All statistical analyses and plotting were performed using R (v.3.6.2). All the tests were two-sided, and  $P < 0.05$  was considered statistically significant.

## Results

### Expression of MMPs in UCEC

Figure 1A depicts the results of the analysis of the TCGA data. Compared with the control UCEC paracancerous tissue, mRNA expression of MMP-1, -3, -8, -9, -10, -11, -12, -13, -15, and -25 was observed to be substantially elevated in tumor tissues, while that of MMP-2, -14, -16, -17, -19, -21, -23B, -24, -26, -27, and -28 was significantly decreased.



**Fig. 1** MMPs mRNA expression levels in UCEC. **A** Differences in MMP mRNA expression between UCEC tumor samples and adjacent normal tissue samples from the TCGA. **B** Differences in MMP mRNA expression between UCEC tumor samples and normal tis-

sue samples from the combined TCGA and GTEx datasets. **C–E**) ROC curves assessing the efficiency of MMPs expression for distinguishing UCEC tumor tissues from non-tumor tissues. (\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ )

These findings were essentially consistent with data from the Genotype-Tissue Expression (GTEx) database where, as shown in Fig. 1B, the mRNA expression of MMP-1, -3, -7, -9, -10, -11, -12, -13, -15, and -20 was significantly higher in tumor tissue compared with healthy tissue, while the levels of MMP-2, -14, -16, -17, -19, -21, -23A, -23B, -24, -25, -27, and -28 were significantly reduced.

ROC curves were then used to assess the ability of MMP expression to differentiate between UCEC and healthy tissues, shown by the area under the curve (AUC) values. AUC

values of 0.5–0.7 = low accuracy, 0.7–0.9 = certain accuracy, and > 0.9 = high accuracy. As shown in Fig. 1C–E, the levels of MMP-1, -9, -12, -15, -19, -23B, and -28 could effectively distinguish between tumor and control tissues, while those of MMP-20, -26, and -27 were less capable, MMP8 was unable, and the other MMP members had some degree of differentiating ability.

Based on these results, 18 MMPs, including MMP-1, -2, -3, -9, -10, -11, -12, -13, -14, -15, -16, -17, -19, -21, -23B, -24, -25, and -28, were selected for subsequent investigation.

## Prognostic value of MMP expression in UCEC

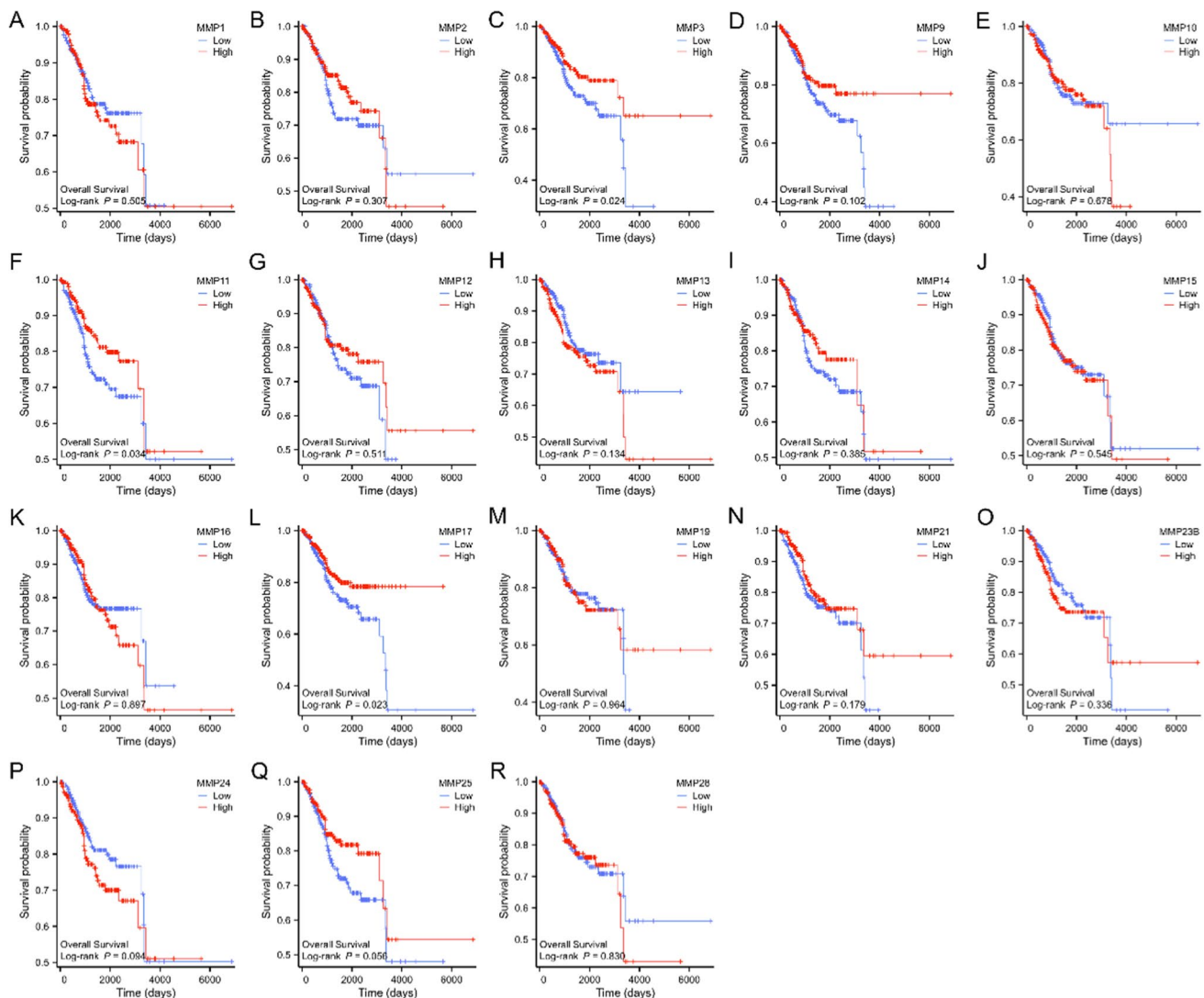
To assess whether MMPs could serve as markers for UCEC prognosis, correlations of MMP mRNA expression with overall survival (OS) rates of UCEC patients were investigated. The Kaplan–Meier analysis showed that reduced expression of MMP3 (Fig. 2C), MMP11 (Fig. 2F), and MMP17 (Fig. 2L) was linked with worse OS. No significant correlations with OS were observed for the other MMP family members ( $P > 0.05$ ).

## Associations of MMPs with clinicopathologic parameters

The association of MMP3, MMP11, and MMP17 expression with the clinicopathological characteristics of UCEC

patients based on TCGA data was assessed. As shown in Table 2, UCEC patients with high and low MMP expression displayed marked differences in clinicopathological features. While no significant differences were seen between MMP levels and most clinicopathological features, MMP11 expression was significantly associated with histological grade and type, primary therapy, age, residual tumor, weight, and menopausal status, and age, histological type and grade, residual tumor, and menopausal status differed significantly between the low and high MMP17-expression groups.

The associations between MMP11 and MMP17 expression and patient clinicopathological characteristics. Kruskal–Wallis rank sum tests showed that MMP11 expression was markedly higher in UCEC patients who were  $\leq 60$  years old (Fig. 3A), had G1/G2 histologic grades (Fig. 3C), were pre-menopausal (Fig. 3E), and



**Fig. 2** Prognostic values of MMPs in UCEC. **A–R** Kaplan–Meier analysis indicated correlations between OS in UCEC patients and mRNA expression of MMPs

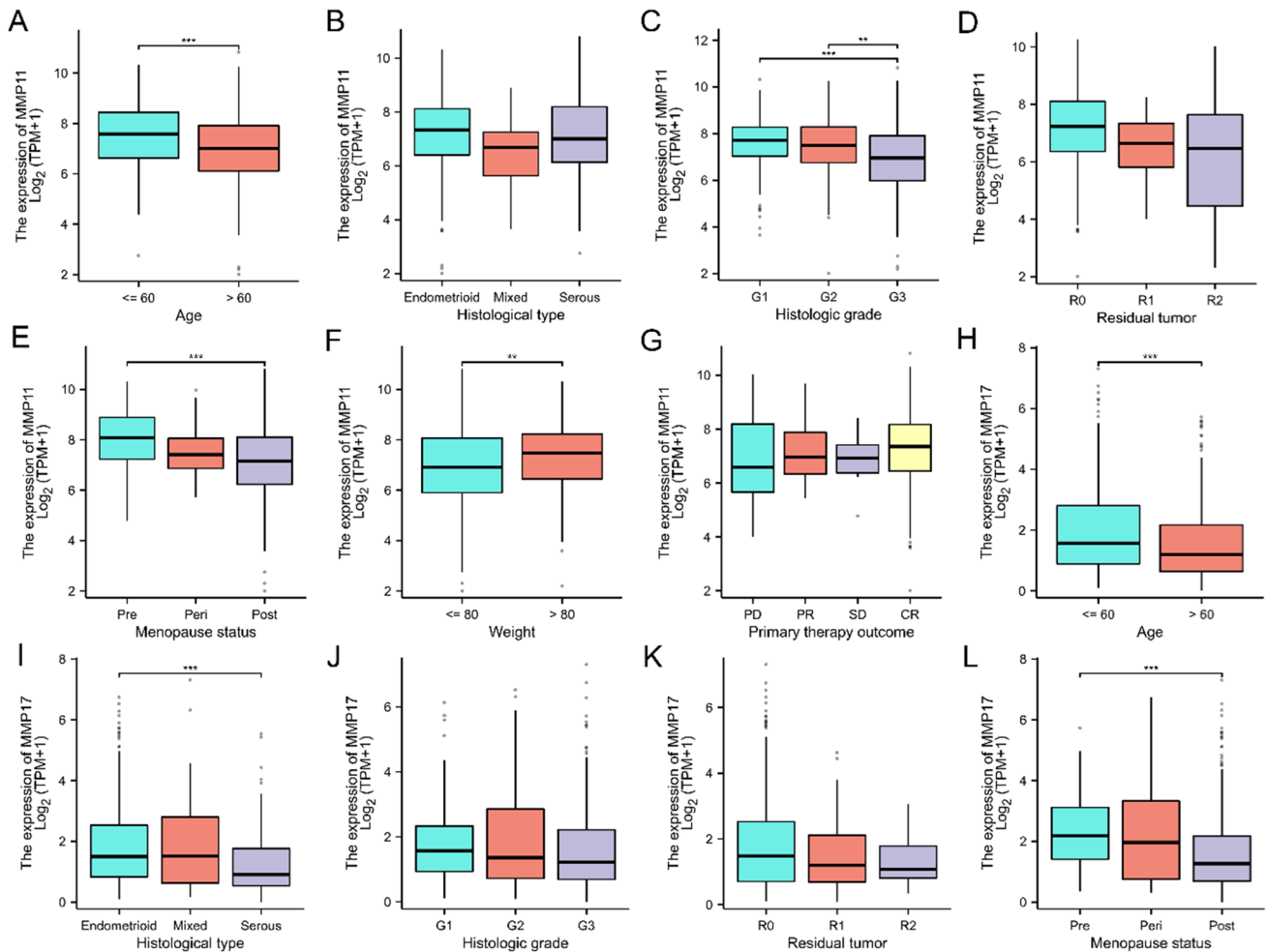
**Table 2** Clinicopathological characteristics of UCEC patients with high- and low- MMPs expression

Characteristics	MMP3 expression			MMP11 expression			MMP17 expression		
	Low	High	<i>p</i>	Low	High	<i>p</i>	Low	High	<i>p</i>
n	277	277		277	277		277	277	
Clinical stage, n (%)			0.1996			0.3933			0.1802
Stage I	174 (31.4%)	169 (30.5%)		169 (30.5%)	174 (31.4%)		162 (29.2%)	181 (32.7%)	
Stage II	19 (3.4%)	33 (6%)		26 (4.7%)	26 (4.7%)		25 (4.5%)	27 (4.9%)	
Stage III	70 (12.6%)	60 (10.8%)		63 (11.4%)	67 (12.1%)		76 (13.7%)	54 (9.7%)	
Stage IV	14 (2.5%)	15 (2.7%)		19 (3.4%)	10 (1.8%)		14 (2.5%)	15 (2.7%)	
Primary therapy outcome, n (%)			0.1052			0.0387			0.3881
PD&SD&PR	23 (4.8%)	15 (3.1%)		24 (5%)	14 (2.9%)		21 (4.4%)	17 (3.5%)	
CR	208 (43.2%)	236 (49%)		203 (42.1%)	241 (50%)		213 (44.2%)	231 (47.9%)	
Race, n (%)			0.1525			0.0842			0.0852
Asian	7 (1.4%)	13 (2.6%)		8 (1.6%)	12 (2.4%)		5 (1%)	15 (2.9%)	
Black or African American	49 (9.6%)	60 (11.8%)		64 (12.6%)	45 (8.8%)		55 (10.8%)	54(10.6%)	
White	199 (39.1%)	181 (35.6%)		181 (35.6%)	199 (39.1%)		191 (37.5%)	189 (37.1%)	
Age, n (%)			0.2393			<0.001			<0.001
≤60	97 (17.6%)	110 (20%)		80 (14.5%)	127 (23%)		81 (14.7%)	126 (22.9%)	
>60	179 (32.5%)	165 (29.9%)		196 (35.6%)	148 (26.9%)		194 (35.2%)	150 (27.2%)	
Weight, n (%)			0.8672			0.004			0.1383
≤80	122 (23%)	121 (22.8%)		137 (25.8%)	106 (20%)		130 (24.5%)	113 (21.3%)	
>80	142 (26.8%)	145 (27.4%)		126 (23.8%)	161 (30.4%)		135 (25.5%)	152 (28.7%)	
Height, n (%)			0.5136			0.4683			0.1051
≤160	120 (22.9%)	127 (24.2%)		126 (24%)	121 (23%)		133 (25.3%)	114 (21.7%)	
>160	143 (27.2%)	135 (25.7%)		133 (25.3%)	145 (27.6%)		130 (24.8%)	148 (28.2%)	
BMI, n (%)			0.5677			0.0533			0.5677
≤30	109 (20.9%)	103 (19.8%)		115 (22.1%)	97 (18.6%)		109 (20.9%)	103 (19.8%)	
>30	151 (29%)	158 (30.3%)		141 (27.1%)	168 (32.2%)		151 (29%)	158 (30.3%)	
Histological type, n (%)			0.2266			0.0095			<0.001
Endometrioid	198 (35.7%)	214 (38.6%)		193 (34.8%)	219 (39.5%)		185 (33.4%)	227 (41%)	
Mixed	15 (2.7%)	9 (1.6%)		18 (3.2%)	6 (1.1%)		11 (2%)	13 (2.3%)	
Serous	64 (11.6%)	54 (9.7%)		66 (11.9%)	52 (9.4%)		81 (14.6%)	37 (6.7%)	
Residual tumor, n (%)			0.4871			0.0151			0.0267
R0	196 (47.2%)	181 (43.6%)		190 (45.8%)	187 (45.1%)		177 (42.7%)	200 (48.2%)	
R1&R2	22 (5.3%)	16 (3.9%)		27 (6.5%)	11 (2.7%)		25 (6%)	13 (3.1%)	
Histologic grade, n (%)			0.8452			<0.001			0.0248
G1	47 (8.7%)	52 (9.6%)		34 (6.3%)	65 (12%)		37 (6.8%)	62 (11.4%)	
G2	61 (11.2%)	60 (11%)		51 (9.4%)	70 (12.9%)		61 (11.2%)	60 (11%)	
G3	164 (30.2%)	159 (29.3%)		184 (33.9%)	139 (25.6%)		171 (31.5%)	152 (28%)	
Tumor invasion (%), n (%)			0.7550			0.1440			0.9644
<50	130 (27.3%)	131 (27.5%)		116 (24.4%)	145 (30.5%)		128 (26.9%)	133 (27.9%)	
≥50	104 (21.8%)	111 (23.3%)		110 (23.1%)	105 (22.1%)		105 (22.1%)	110 (23.1%)	
Menopause status, n (%)			0.7355			0.0013			0.0002
Pre&Peri	25 (4.9%)	27 (5.3%)		15 (3%)	37 (7.3%)		14 (2.8%)	38 (7.5%)	
Post	230 (45.4%)	225 (44.4%)		238 (46.9%)	217 (42.8%)		243 (47.9%)	212 (41.8%)	
Diabetes, n (%)			0.5852			0.1369			0.724
No	166 (36.6%)	163 (36%)		152 (33.6%)	177 (39.1%)		160 (35.3%)	169 (37.3%)	
Yes	59 (13%)	65 (14.3%)		67 (14.8%)	57 (12.6%)		58 (12.8%)	66 (14.6%)	
Hormones therapy, n (%)			0.9768			0.9180			0.1377
No	147 (42.5%)	152 (43.9%)		136 (39.3%)	163 (47.1%)		137 (39.6%)	162 (46.8%)	



**Table 2** (continued)

Characteristics	MMP3 expression			MMP11 expression			MMP17 expression		
	Low	High	<i>p</i>	Low	High	<i>p</i>	Low	High	<i>p</i>
Yes	23 (6.6%)	24 (6.9%)		21 (6.1%)	26 (7.5%)		27 (7.8%)	20 (5.8%)	
Radiation therapy, n (%)			0.2630			0.9847			0.6809
No	144 (27.2%)	137 (25.9%)		138 (26.1%)	143 (27%)		141 (26.7%)	140 (26.5%)	
Yes	115 (21.7%)	133 (25.1%)		122 (23.1%)	126 (23.8%)		120 (22.7%)	128 (24.2%)	



**Fig. 3** Relationship between MMP expression and various clinicopathological factors in UCEC. **A–G** MMP11 expression in UCEC patients of different ages (**A**), histological types (**B**), histological grades (**C**), residual tumor (**D**), menopausal status (**E**), weights (**F**),

and primary therapy outcomes (**G**). **H–L** MMP17 expression in UCEC patients of different ages (**H**), histological types (**I**), histological grades (**J**), residual tumor (**K**), and menopausal status (**L**). (\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ )

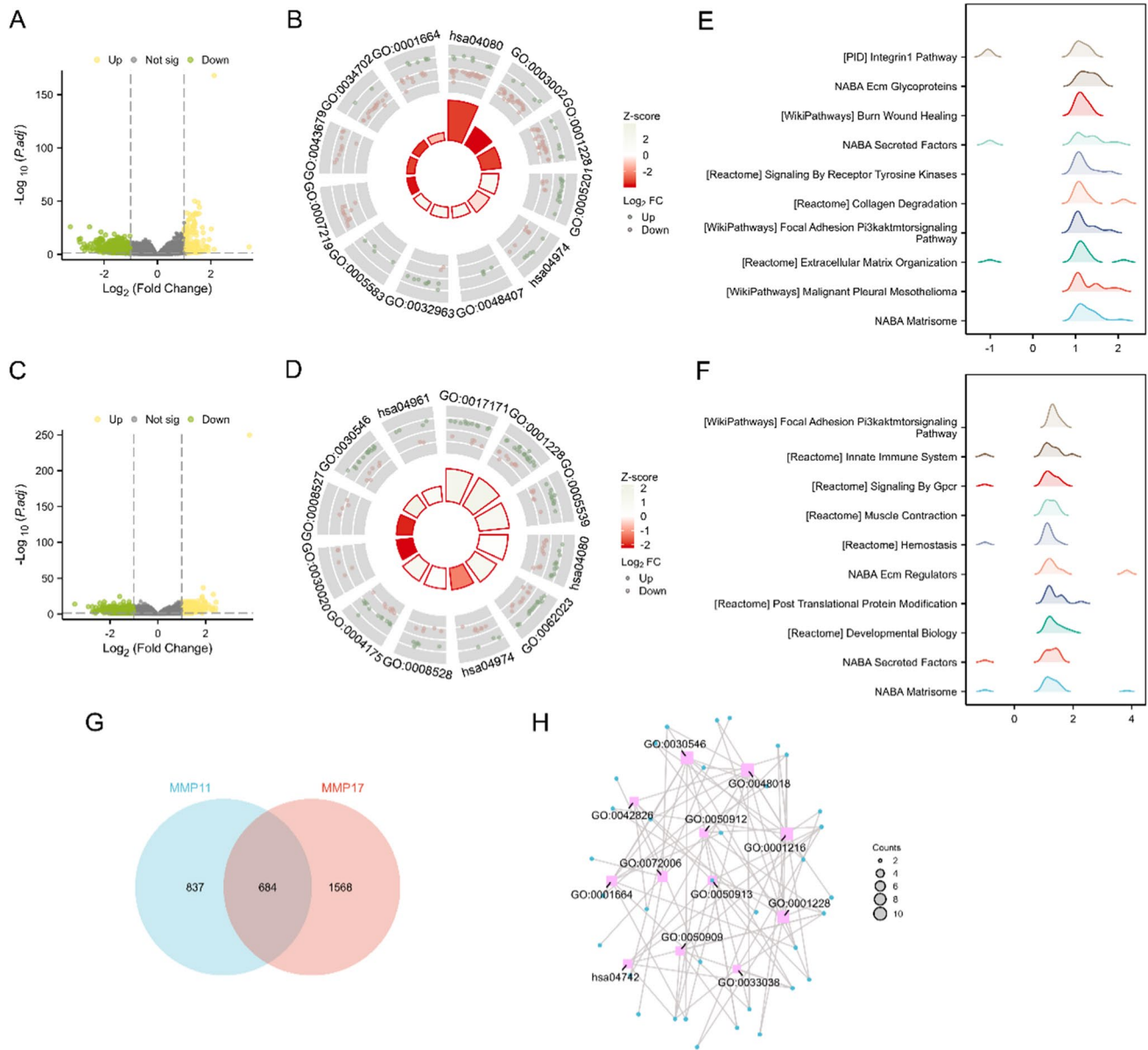
weighed  $> 80$  kg (Fig. 3F). Expression of MMP17 was substantially higher in UCEC patients  $\leq 60$  years old (Fig. 3H), with endometrioid-type tumors (Fig. 3I), and were pre-menopausal (Fig. 3L). The ability of MMP11 and MMP17 to differentiate between tumor and non-tumor tissues were then validated in the GEO datasets (GSE115810 and GSE36389) using ROC analysis (Supplementary Material Figure 1).

### Functional and pathway enrichment analyses of DEGs between the low and high MMP-expression groups

The potential roles of MMP11 and MMP17 in UCEC was assessed by analyzing DEGs between the low- and high-expression groups. A total of 1529 DEGs (of which 188

and 1341 were up- and down-regulated, respectively) were identified between the low and high MMP11-expression groups (Fig. 4A). GO functional enrichment indicated that MMP11 was significantly associated with “collagen metabolic process (GO:0032963)”, “regionalization (GO:0003002)”, “fibrillar collagen trimer (GO:0005583)”, “axon terminus (GO:0043679)”, “ECM structural constituent (GO:0005201)”, “Notch signaling pathway (GO:0007219)”, “ion channel complex (GO:0034702)”,

“activity of DNA-binding transcription activator, RNA polymerase II- specific (GO:0001228)”, “G protein-coupled receptor binding (GO:0001664)”, and “platelet-derived growth factor binding (GO:0048407)”, while KEGG analysis revealed the greatest enrichment in the “neuroactive ligand-receptor interaction (hsa04080)”, and “protein digestion and absorption (hsa04974)” pathways (Fig. 4B). Altogether, 2291 DEGs (329 and 1962 up- and down-regulated, respectively) were identified between the low and



**Fig. 4** Functional enrichment analysis of DEGs in UCEC. **A** Volcano plots of total DEGs between the low and high MMP11-expression groups. Yellow color indicates upregulated genes, green indicates downregulated genes, and black indicates DEGs below the cutoff criteria. **B** Enriched GO terms and KEGG classifications of MMP11-related DEGs. **C** Volcano plots of total DEGs between the low and

high MMP17-expression groups. **D** Enriched GO terms and KEGG classifications of MMP17-related DEGs. **E** MMP11-related signaling pathways based on GSEA. **F** GSEA-based MMP17-related signaling pathways. **G** Venn diagram of DEGs between MMP11 and MMP17. **H** Enriched GO terms and KEGG classifications of intersecting DEGs between MMP11 and MMP17

high MMP17-expression groups (Fig. 4C). The results of the GO functional enrichment showed that MMP17 was significantly associated with “collagen-containing ECM (GO:0062023)”, “ECM structural constituent conferring tensile strength (GO:0030020)”, “serine hydrolase activity (GO:0017171)”, “taste receptor activity (GO:0008527)”, “G protein-coupled peptide receptor activity (GO:0008528)”, “endopeptidase activity (GO:0004175)”, “glycosaminoglycan binding (GO:0005539)”, “DNA-binding transcription activator activity, RNA polymerase II-specific (GO:0001228)”, and “signaling receptor activator activity (GO:0030546)”. KEGG analysis indicated that the DEGs were mainly involved in “Neuroactive ligand-receptor interaction (hsa04080)”, “Endocrine and other factor-regulated calcium reabsorption (hsa04961)”, and “Protein digestion and absorption (hsa04974)” (Fig. 4D).

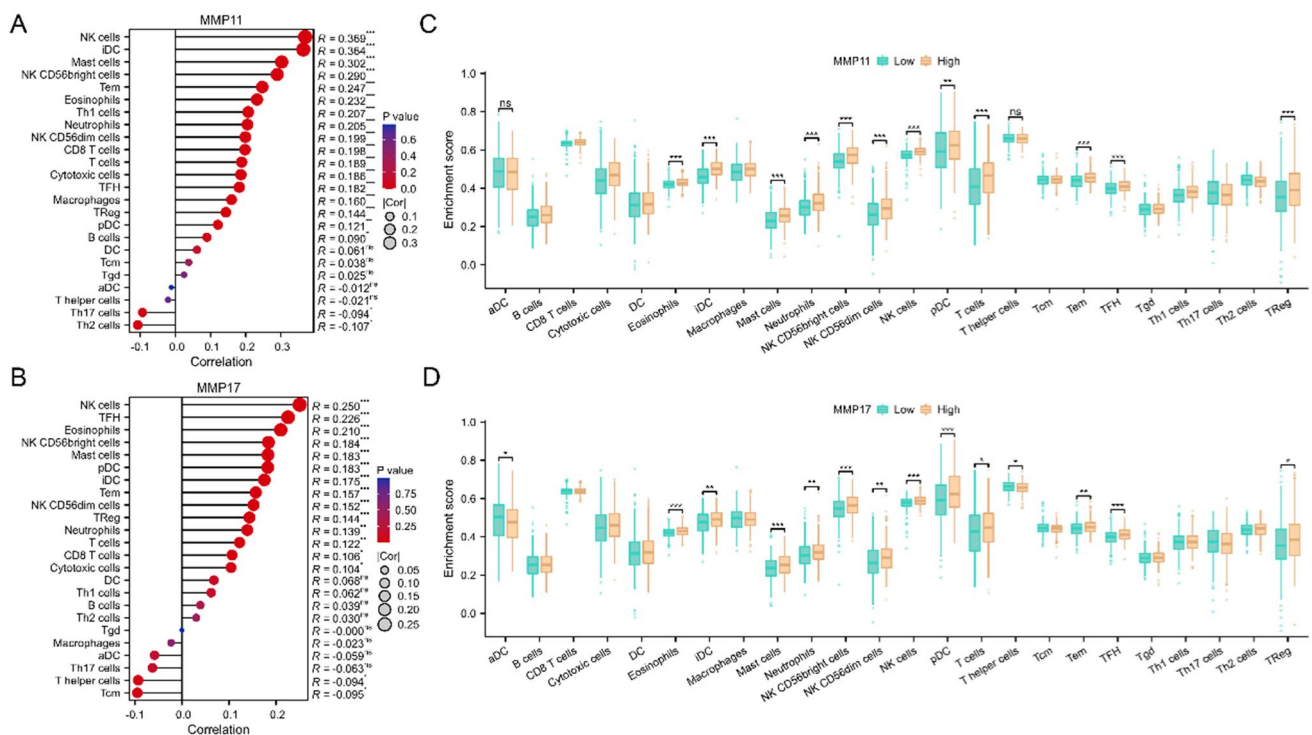
To further assess possible biological pathways by which MMP11 and MMP17 influenced UCEC, a GSEA pathway analysis was performed. This showed that MMP11 expression was associated with cancer-related pathways, such as “matrisome”, “malignant pleural mesothelioma”, “ECM organization”, “focal adhesion pi3kaktmtor signaling pathway”, and “integrin1 pathway” (Fig. 4E). MMP17 expression was also associated with cancers related pathways, such as “matrisome”, “focal adhesion pi3kaktmtor signaling

pathway”, “post-translational protein modification”, “signaling by gpcr”, and “innate immune system” (Fig. 4F).

Six hundred and eight-four DEGs that overlapped between MMP11 and MMP17 were selected, and their functional enrichment analysis revealed that they were primarily associated with “identification of chemical stimulus linked with the sensory taste perception (GO:0050912)”, “RNA polymerase II-specific DNA-binding transcription activator activity(GO:0001228)”, “activity of signaling receptor activator (GO:0030546)”, “histone deacetylase binding (GO:0042826)”, and “G protein-coupled receptor binding (GO:0001664)”.

### Correlations between MMP expression with tumor immune-infiltrating cells (TIICs)

The associations of MMP expression with the infiltration of 24 different TIICs in the UCEC tumor microenvironment (TME) were assessed. The expression of MMP11 was found to be positively correlated with most TIICs, with correlation coefficients  $R > 0.3$  for NK, interstitial dendritic, and mast cells (Fig. 5A). The expression of MMP17 was also positively correlated with most TIICs, but no correlations  $> 0.3$  were observed (Fig. 5B). Furthermore, the enrichment scores of immune cells in the low -and high-MMP expression.



**Fig. 5** Correlation of MMP expression with TIICs in the UCEC TME. (A–B) Correlations between MMP11 (A) and MMP17 (B) expression with the indicated immune cells. Dot size=absolute correlation coefficient (R), and the color gradient from blue to red=low

to high  $P$  value. C–D Comparisons of TIICs between low and high MMP11 (C) and MMP17 expression groups (D). \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$



groups were assessed, showing that both high-expression groups had higher/ levels of infiltration of immune cells, including eosinophils, NK CD56bright cells, interstitial dendritic cells,

=]K CD56dim cells, mast cells, plasmacytoid dendritic cells, T cells, neutrophils, and Tem, TFH, NK, and Treg cells (Fig. 5C, D). Additionally, the high MMP17-expression group had lower infiltration of  $\alpha$ DC and T helper cells (Fig. 5D).

## Discussion

MMP proteins are mainly involved in physiological processes associated with ECM breakdown. Several MMP family members, such as MMP1, are known to be involved in cancers, where the gene is largely expressed in human oral and cervical squamous cell carcinoma and promotes tumor cell growth and motility [15, 16]. It has been suggested that high MMP14 expression in muscle-invasive bladder and colorectal cancers is linked with poor prognosis, while low expression inhibits metastasis in breast and gastric cancer cells [17–20]. In addition, MMP-2, -9, and -16+ are involved in the development of multiple cancers [21–24]. However, the specific roles of MMPs in UCEC remain undetermined. In this investigation, bioinformatics tools were used to analyze the the expression of MMPs, their prognostic value, potential functions, mechanisms, and associations with immune cell infiltration in UCEC.

Altogether, 22 MMP family members were found to be differentially expressed between UCEC tumor and healthy tissues, where the mRNA expression of MMP-1, -3, -7, -9, -10, -11, -12, -13, -15, and -20 was substantially enhanced in tumor tissues, while that of MMP-2, -14, -16, -17, -19, -21, -23A, -23B, -24, -27, and -28 were notably reduced and no consistent expression of MMP-25 was seen in the two databases. These results, together with those of the ROC analysis, led to the selection of 18 MMPs for survival analysis, finding that the expression of MMP-3, -11, and -17 were significantly correlated with OS in UCEC patients. Since there was no significant correlation between MMP3 expression and patient clinicopathological features, MMP11 and MMP17 were selected for subsequent analyses.

MMP11 and MMP17 are major members of the MMP family. Research has shown that they are critical in the development and progression for various cancers, including breast, gastric, lung, and ovarian cancers [25–28]. MMP11 is strongly expressed in breast cancer, and its high expression is associated with both metastasis and poorer prognosis [29]. MMP11 expression is also upregulated in uveal melanoma and is linked with shorter OS and disease-free survival [30]. MMP17 expression is increased in ovarian cancer where it may promote carcinogenesis by disrupting the ECM and

has diagnostic and prognostic value for clinical outcomes [28]. Here, MMP11 expression was elevated in UCEC, and its elevation was linked with better OS, while MMP17 showed reduced expression, which was found to be linked with poor OS, in contrast to the findings of other studies. Furthermore, MMP11 expression was markedly elevated in UCEC patients who were  $\leq 60$  years old, had lower histological grades, were pre-menopausal, and  $> 80$  kg weight. Expression of MMP17 was significantly increased in UCEC patients who were  $\leq 60$  years old, pre-menopausal, and had cancers of the endometrioid type. It was hypothesized that high MMP11 and MMP17 expression has anti-tumor effects. Therefore, the DEGs in the low and high MMP11 and MMP17 expression groups were investigated. Functional enrichment analysis showed that these DEGs were mainly linked with ECM construction and degradation, glucose metabolism, and various cancer signaling pathways, such as the PI3K-AKT pathway. In addition, an association between the expression of MMP11 and MMP17 and immune cell infiltration was identified. Tumor tissues with high MMP11 and MMP17 expression were associated with high levels of infiltrating NK, mast, and NK CD56bright cells. NK cells in solid tumors mainly infiltrate the tumor stroma and can modulate tumor growth by interacting directly with tumor cells or other immune cells [31]. Studies have shown that increased tumor NK cell infiltration in colon cancer and metastatic cutaneous melanoma is associated with higher survival rates [32, 33]. Therefore, the presence of NK cells in the TME may be associated with good prognosis. Whether mast cells promote tumor growth or anti-tumor immune responses is still controversial. The literature suggests that mast cells can secrete various cytokines, such as IL-3, IL-6, and TNF- $\alpha$  [34]. TNF- $\alpha$  can prevent vascular growth by inhibiting endothelial cell proliferation, causing tumor tissue necrosis, and abrogating and preventing malignant tumor metastasis [35]. Thus, the infiltration of tumor tissue by mast cells has an anti-tumor and host-protective role. The NK CD56bright cell subset is often described as regulatory. NK CD56bright cells are activated by cytokines such as IL-5 and are cytotoxic and can enhance the anti-tumor response [36, 37]. In our investigation, patients with high expression of MMP11 or MMP17 had longer OS, which may be due to the higher infiltration levels of NK cells, mast cells, and NK CD56bright cells with anti-tumor effects in their tumor tissues, which in turn delayed further tumour progression and improved the prognosis of these patients. Therefore, MMP11 and MMP17 may exert anti-tumor effects by altering the immune cell infiltration of tumor tissues.

To the best of our knowledge, this is the first investigation to assess the relationship between all MMPs and UCEC. However, there are some limitations to the study. (1) The results differ from those in the literature, and thus relevant experiments should be conducted to verify these results. (2)

The TCGA data were not sufficiently comprehensive, and more data should be included for effective analysis.

## Conclusions

The results indicated that high MMP11 and MMP17 expression was associated with better prognosis and was correlated with immune cell infiltration. Therefore, MMP11 and MMP17 could be used as effective biomarkers and therapeutic targets for UCEC. However, further investigations are needed to verify these results and strengthen their application.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s12094-023-03284-5>.

**Authors' contributions** Yanhui Zhang participated in the design of this study, and written this papers. Jing Wang and Yuqin Fan participated in the design of this study, and they both performed the statistical analysis. Fangfang Lang and Fengping Fu carried out the study and collected data. Quanying Liu contributed to the study conception and design. Yanhui Zhang and Jing Wang share first authorship.

**Data availability** Data in this study was obtained from TCGA public database and the acquisition and application method complied with corresponding database guidelines and policies.

## Declarations

**Conflict of interest** There are no conflicting interests between the authors.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** For this type of study formal consent is not required.

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