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Significance of Matrix Metalloproteinase-12 in Cervical Cancer: A Bioinformatics Analysis for Diagnosis, Prognosis

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Abstract: *Introduction:* Matrix metalloproteinase-12 (MMP12) plays an important role in suppressing tumor growth. MMP12 is associated with cervical squamous cell carcinoma (CESC). However, the correlation between MMP12 in conjunction with immune cell infiltration and its impact on the prognosis of CESC is unclear. Therefore, this research aimed to examine the transcriptional profile and predictive significance of MMP12 in CESC. *Materials and methods:* Gene expression patterns and clinical profiles of patients diagnosed with CESC were analyzed using the Cancer Genome Atlas database. Statistical analyses were performed to compare MMP12 expression between CESC and healthy cervical tissues. Functional enrichment was also performed. MMP12 methylation was analyzed using the EWAS database. Prognostic assessment was performed using Cox regression and Kaplan–Meier analyses. A nomogram was developed for forecasting overall survival. *Conclusions:* This research underscores the potential of MMP12 as a trusted indicator for diagnosing and predicting the expected outcome of CESC. Furthermore, MMP12 serves as a critical element in tumor invasion and evasion of the body's protective system, highlighting its significance in the development of targeted therapies for CESC.

Keywords: Cervical cancer; Matrix metalloproteinase-12; Prognosis; Methylation

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1. Introduction

Cervical squamous cell carcinoma (CESC) presents a notable global risk to women's health and is a leading contributor to cancer-related fatalities in women. In 2020, an estimated 604,127 CESC cases were reported globally, resulting in 341,831 deaths. The adjusted occurrence rate stood at 13.3 cases per 100, 000 woman–years, and the fatality rate was 7.2 deaths for every 100,000 woman–years [1]. Extensive research has been conducted to elucidate the etiology, development, and therapeutic interventions of CESC. Recently, progress in detection and treatment modalities has resulted in a gradual decline in CESC mortality [2]. However, the prognosis of numerous patients remains uncertain, emphasizing the urgent demand for new strategies in the diagnosis and treatment of CESC. Current research focuses on elucidating the impact

of matrix metalloproteinase-12 (MMP12) on CESC using a combined informatics strategy supported by experimental verification.

MMP12 is a crucial enzyme of interest in CESC research because of its role in breaking down the extracellular matrix, a process essential for tumor invasion and metastasis [3–4]. MMP12 expression increases significantly in CESC tissues but not in healthy cervical tissues, suggesting a potential connection between MMP12 and cancer progression [5–6]. Elevated MMP12 levels have been linked to more advanced tumor phenotypes and less favorable prognosis in patients suffering from CESC [7]. MMP12 breaks down basement membranes and modulates immune responses in the tumor microenvironment [8–9]. However, the specific mechanisms by which MMP12 influences CESC progression and its association with patient outcomes and immune cell invasion remain unknown. Therefore, this study aimed to fill this knowledge gap through extensive bioinformatic analysis complemented by experimental validation.

The principal focus of this research was to investigate the transcriptional signature and predictive significance of MMP12 in CESC employing bioinformatic tools. Through the application of advanced bioinformatics methodologies, the purpose of this study was to explore the correlation between MMP12 levels and various clinical and pathological characteristics, their significance for patient prognosis, and the degree of immune cell invasion in CESC tumors.

2. Materials and methods

2.1. Data collection from The Cancer Genome Atlas database

mRNA expression information and clinical records were sourced from prominent databases. The Cancer Genome Atlas (TCGA) database—a collaborative project involving multiple institutions—was used to collect extensive molecular information from malignant cervical tissue samples. The GTEx database was used to gather vital genomic and transcriptional data from healthy cervical tissues. Combining the data from both databases resulted in a comprehensive and varied dataset encompassing malignant and non-cancerous cervical tissue types. This enabled a detailed evaluation of MMP12 mRNA expression profiles in individuals with CESC as well as an investigation into potential associations with clinical outcomes.

2.2. Differential expression analysis of MMP12

A detailed bioinformatic analysis was conducted to examine the impact of MMP12 on CESC. Patients diagnosed with CESC in the TCGA database were categorized into two separate groups based on high and low MMP12 expression levels. Using the R package DESeq2, differentially expressed genes (DEGs) with a corrected P-value < 0.05 and a log2-fold change (FC) > 2 were identified between the groups [10]. Spearman's correlation analysis is a statistical method that measures the magnitude and indicates the direction of the monotonic associations between pair variables [11]. Spearman's correlation analysis of the top eight DEGs was conducted in order to further elucidate the interaction between MMP12 and gene level.

2.3. Gene set enrichment analysis

Gene Set Enrichment Analysis (GSEA) was used to contextualize RNA sequencing data from the TCGA database. This computational method—which is accessible through the MSigDB website—aids in the standardization and interpretation of sequencing data. The potential biological functions associated with MMP12 were investigated using GSEA. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were employed to determine relevant biological processes, molecular functions, and cellular components related to MMP12 expression. These analyses were performed utilizing an R-based gene clustering analyzer. GO terminology is organized into three primary domains: cellular components, molecular functions, and biological processes, which form a detailed system for decoding gene functionality. KEGG pathway analysis was carried out to investigate the particular molecular pathways in which MMP12 may be involved, providing insights into intricate molecular interactions and signaling cascades. For

reliable enrichment outcomes, strict standards were maintained: a false discovery rate (FDR) of < 0.05 and a nominal *P*-value of < 0.05. These benchmarks pinpointed statistically significant enrichments, suggesting that the potential biological functions and pathways linked to MMP12 are not likely a result of random variation.

2.4. DNA methylation analysis

The role of MMP12 methylation in CESC progression was investigated. By correlating clinical outcomes with methylation data, this research aimed to ascertain whether MMP12 methylation is a prognostic indicator for cervical tumors. This analysis was performed by investigating the methylation status of the MMP12 promoter region, which plays a vital role in regulating MMP12 levels, using the EWAS database [12]. This resource offers an in-depth analysis of cancer transcriptomic data, allowing for detailed exploration of gene expression patterns. Additionally, the UALCAN database, an online tool that supports survival analysis with a focus on DNA methylation, was used to assess the clinical relevance of MMP12 methylation levels [13].

2.5. Nomogram validation

Multivariate Cox proportional hazards regression analysis was carried out to forecast the overall survival (OS) probability in patients with CESC. A nomogram including significant prognostic factors was constructed, which visually illustrated the association between these factors and the likelihood of survival. A calibration plot was used to compare the actual and predicted survival rates and to evaluate the precision of the predictions. Additionally, the concordance index was calculated to determine the concordance between the predicted and observed survival, which signified the predictive power of the nomogram for OS. The R package RMS was used to generate nomograms and calibration plots to validate the predictive accuracy of the model, and the time ROC package was used to carry out time-dependent receiver operating characteristic (ROC) curve analysis. This approach enabled the evaluation of the predictive capability of the model at various time points and assessment of its reliability in predicting survival probabilities across different disease stages, thereby contributing to the clinical utility and credibility of the predictions.

2.6. Survival analysis

Kaplan–Meier survival analysis and the log-rank test were utilized for analyzing the survival data of patients with CESC. The threshold was established using the minimum *P*-value associated with MMP12 levels. Univariate Cox regression analysis was performed to examine the influence of various clinical parameters on individual outcomes. The R package ggplot2 was employed to generate forest plots to illustrate these results, offering a clear and informative illustration of the univariate Cox regression results, and demonstrating the efficacy of clinical variables on the survival indices of patients with cervical tumors.

2.7. Statistical analysis

Analytical procedures were conducted utilizing SPSS version 26.0 (IBM, Armonk, NY, USA). The Wilcoxon signed-rank test was employed to evaluate disparities in expression levels between CESC and normal tissue specimens. One-way analysis of variance was conducted to assess differences between the two groups. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. High MMP12 expression in CESC

Pan-cancer analysis revealed that MMP12 expression was elevated in most tumor types contrasted with that in normal tissues, including breast invasive carcinoma, lung adenocarcinoma, and stomach adenocarcinoma (**Figure 1A**). MMP12 expression in CESC was notably higher than that in healthy tissue specimens (**Figure 1B**). ROC curve analysis suggested

that MMP12 expression in patients with CESC effectively predicted the occurrence of CESC. The area under the curve (AUC) for MMP12 expression, which indicated its capacity to distinguish between individuals with and without cervical carcinoma, was notably high at 0.956 (**Figure 1C**). These results suggest that MMP12 is a reliable indicator for the diagnostic assessment of CESC, facilitating early detection and enhancing treatment options.

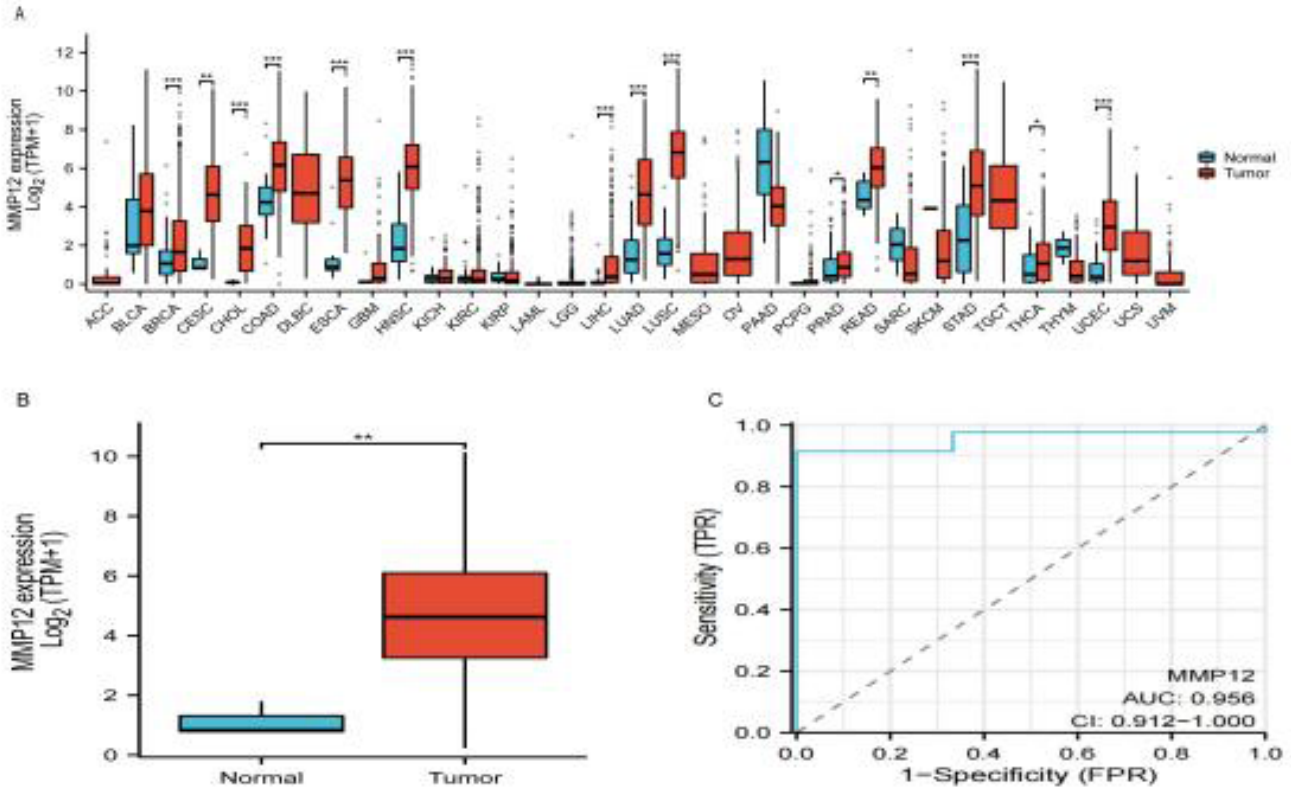

Figure 1. Matrix metalloproteinase-12 expression in tumors. (A) Matrix metalloproteinase-12 (MMP12) was highly expressed in many solid tumors. (B) MMP12 was highly expressed in cervical squamous cell carcinoma (CESC). (C) The receiver operating characteristic curve area was 0.956, indicating that MMP12 is a diagnostic biomarker of CESC. *P*-values were calculated using a two-tailed unpaired Student's t-test, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

3.2. Prognostic value

Individuals with high MMP12 expression experienced a reduced OS than patients with low MMP12 expression (**Figure 2A**). Similarly, the progression-free interval was shorter in the high MMP12 expression group than in the low MMP12 expression group (**Figure 2B**). Univariate Cox regression analysis identified several clinical features as pathogenic elements affecting OS, including stages T3, T4, N1, M1, and T4 (**Figure 2C**). These findings suggest that MMP12 may play an indicative role in predicting disease progression, treatment efficacy, and patient survival.

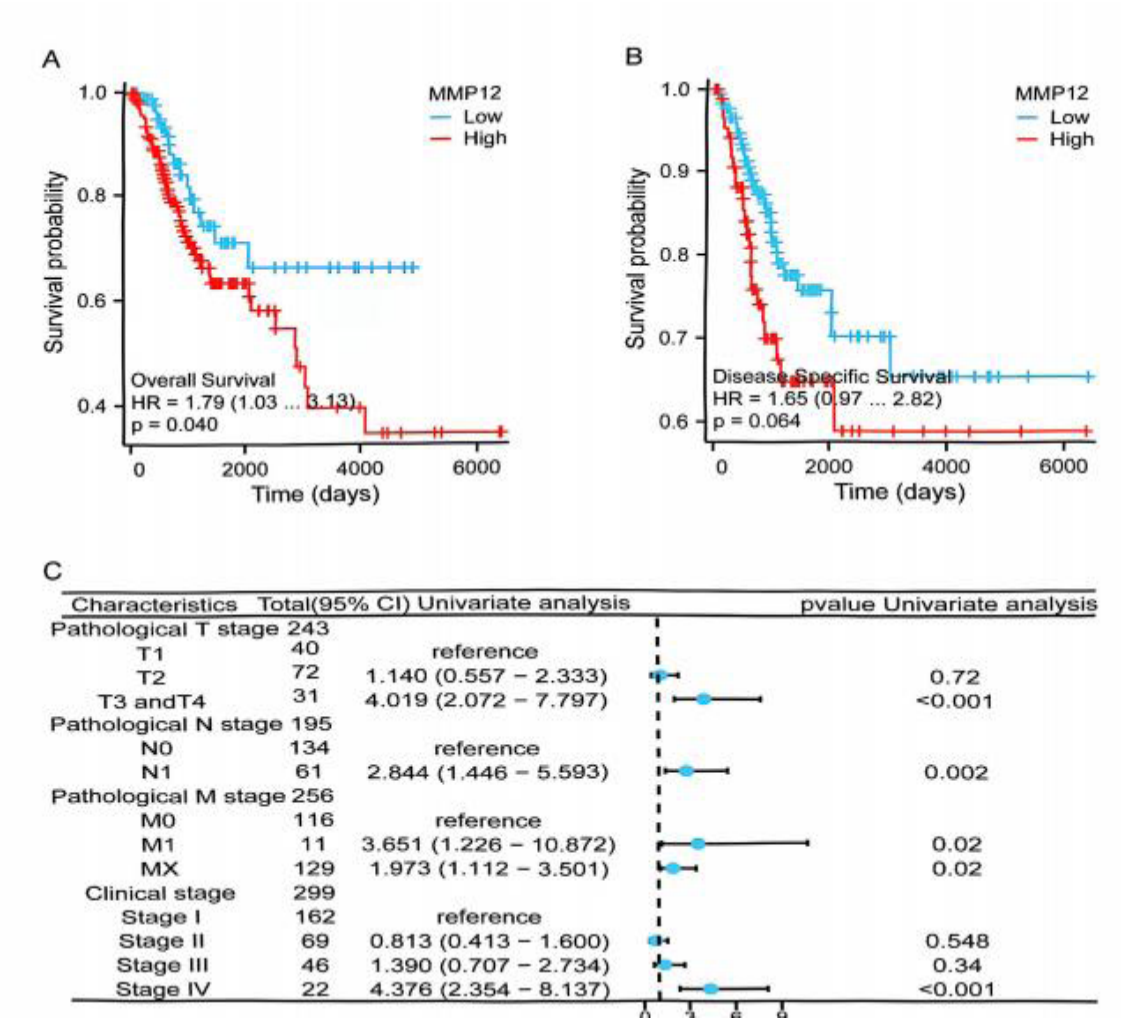

Figure 2. The effect of MMP12 expression on the prognosis of patients with CESC was evaluated using Kaplan–Meier analysis. (A) Overall survival (OS) and (B) disease-free survival for patients with CESC and high-vs low-MMP12 expression. (C) Forest map of OS of patients with CESC based on univariate Cox analysis.

3.3. Analysis of functional enrichment in DEGs

In CESC, 214 coding genes showed differential expression between the high and low MMP12 expression cohorts. Of these, 32 genes (14.9%) were positively regulated, and 182 were downregulated (85.1%; adjusted *P*-value < 0.05, | Log 2 FC | > 2; **Figure 3A**). This study centered on the top eight DEGs and their associations with MMP12. The FAT4, C8orf86, COLCA1, KIF19, ZNF681, ACADSB, STK40, and RPS2P4 genes were selected for further analysis, and their relationship with MMP12 is shown in **Figure 3B**. GO and KEGG analyses revealed that biological processes were predominantly enriched in nuclear division, mitotic nuclear division, and the segregation of mitotic sister chromatids. Major enrichments in cellular components were observed in the spindle, chromosome centromeric region, and mitotic spindle. The enriched terms for molecular functions were tubulin binding, microtubule binding, and microtubule motor activity (**Figure 3C–E**). Significant pathway enrichment was identified through KEGG pathway analysis, including the cell cycle, cellular senescence, and oocyte meiosis. GSEA showed that elevated MMP12 levels were significantly clustered in the biological processes associated with the transport of small molecules and disorders of transmembrane transporters (**Figure 3F, G**). Gene enrichment analysis can help researchers better understand the mechanism of MMP12-mediated occurrence and development of CESC, providing potential targets for drug development and therapeutic strategies.

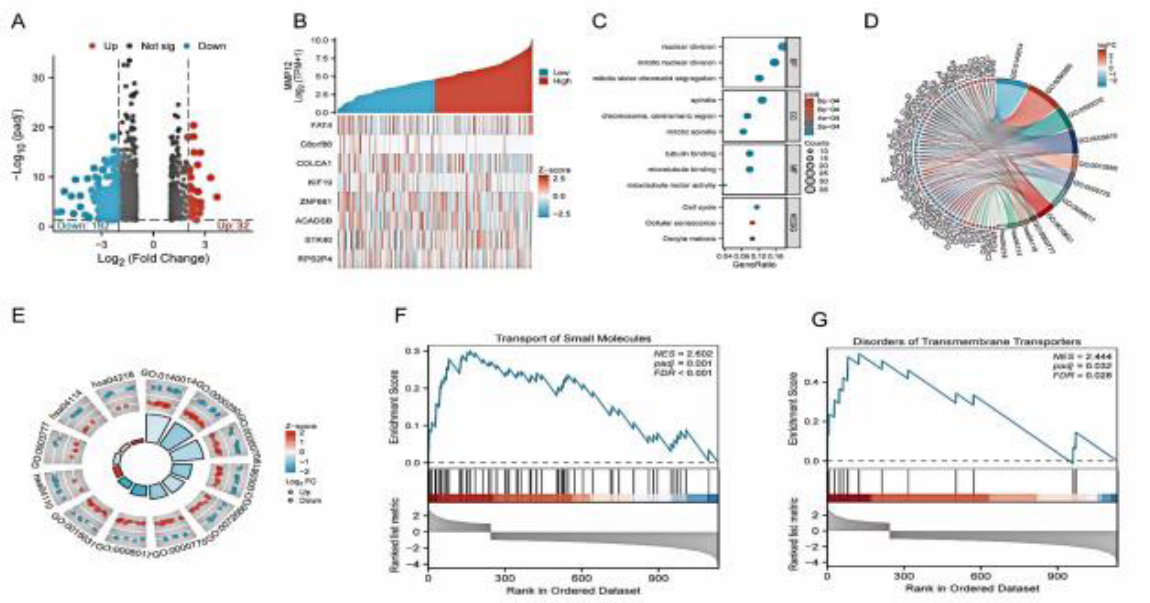

Figure 3. Differentially expressed genes related to MMP12 and its functional enrichment analysis using Gene Set Enrichment Analysis (GSEA), Gene Ontology (GO), and the Kyoto Encyclopedia of Genes and Genomes (KEGG). (A) Blue and red dots indicate the vitally down- and upregulated differentially expressed genes (DEGs) in the volcano plot, respectively. (B) The top eight DEGs positively correlated with the MMP12 expression. (C–E) GO KEGG of DEGsand (F–G) GSEA.

3.4. Association between MMP12 expression and methylation status

Online services, such as the EWAS database, indicated a significant decrease in DNA methylation levels at the MMP12 promoter in CESC tissue relative to cervical epithelial tissue ($P < 0.001$; **Figure 4A**). A predominant number of methylation spots within the MMP12 DNA arrangement were hypomethylated in CESC. Individuals with CESC and low MMP12methylation demonstrated lower OS rates compared to those with elevated MMP12 methylation levels (**Figure 4B, C**). In some cases, MMP12 methylation may occur before the clinical symptoms of a disease appear; therefore, it can be used for the early detection of CESC.

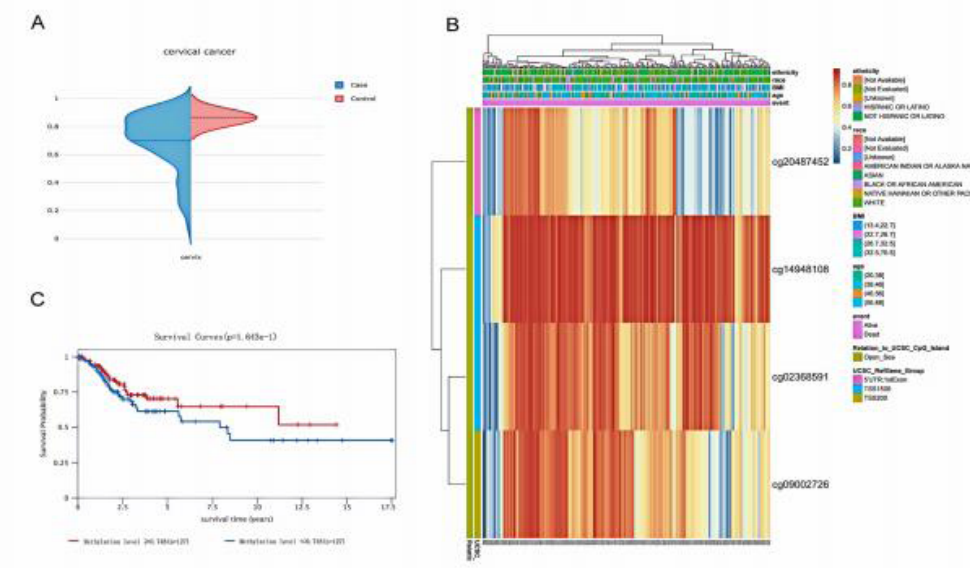

Figure 4. DNA promoter methylation level of MMP12 and its effect on the prognosis of patients with CESC. (A) The promoter methylation level of MMP12 in CESC tissues was lower than that in normal cervical tissue. (B) Correlation between MMP12 mRNA expression and methylation level. (C) Kaplan–Meier survival curves for MMP12 methylation sites. *P*-values were calculated using the two-tailed unpaired Student's t-test, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

3.5. Construction and validation of a nomogram

As the points on the diagram increased, reflecting the accumulation of more deleterious prognostic indicators, the condition of patients with CESC worsened (**Figure 5A**). Increased aggregate point values indicated worse clinical outcomes. The effectiveness and consistency of the predictive capabilities of the nomogram were tested using calibration curve analysis (**Figure 5B–D**). This analysis indicates that MMP12 significantly influences the prognosis of patients with CESC as an independent prognostic factor.

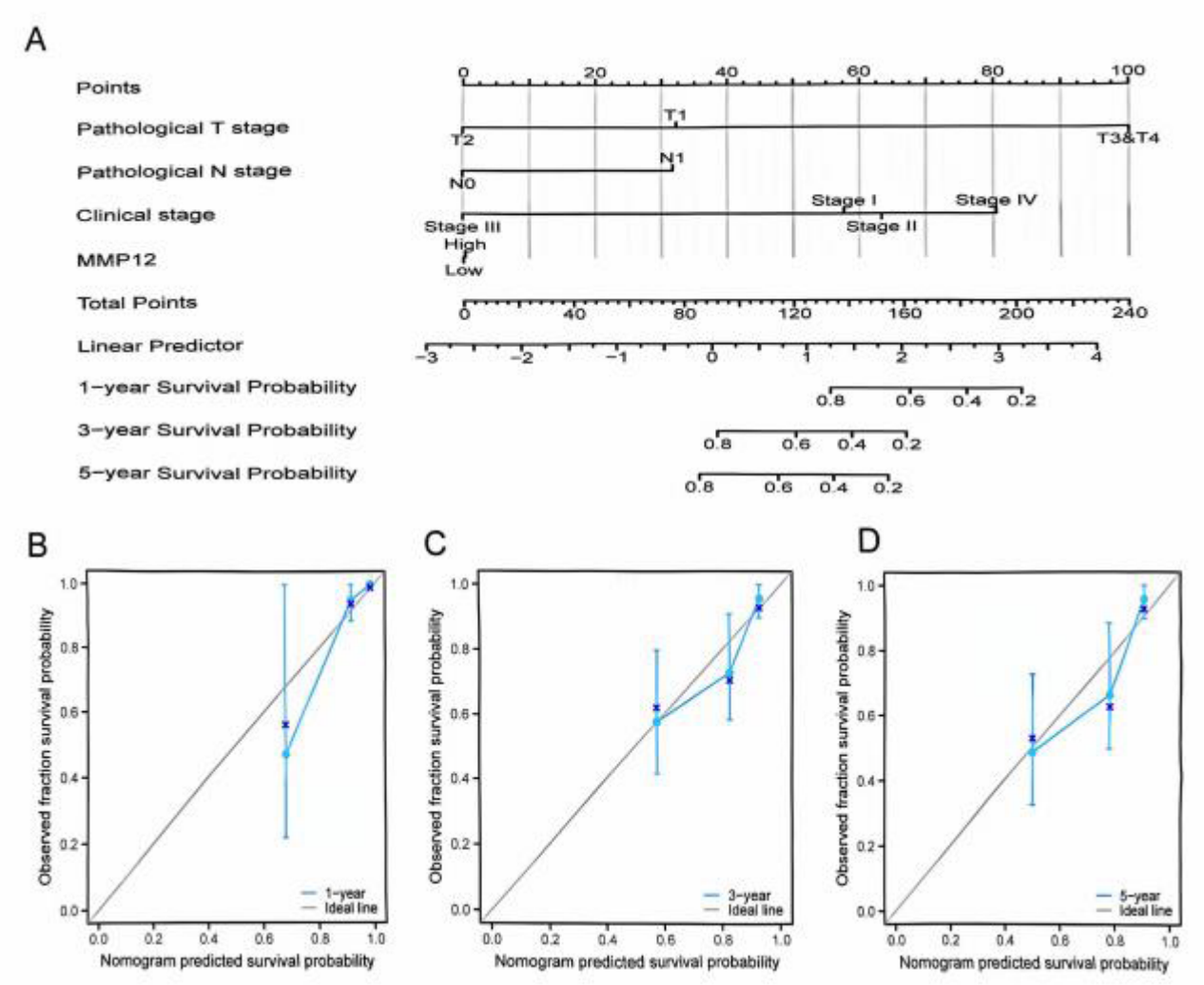

Figure 5. Calibration curves and a nomogram to predict the OS rates of patients with CESC. (A) A nomogram chart shows data of the OS rates of patients with CESC at specific time intervals, such as one, three, and five years. (B–D) Calibration curves are graphical tools used to predict the survival rates of patients with cancer at specific time points.

4. Discussion

CESC is diverse; therefore, existing predictors, such as grade, human papillomavirus status, and tumor size, exhibit limitations in accurately predicting patient outcomes. Consequently, the identification of novel biomarkers that enhance prognosis predictions and guide individualized therapeutic strategies is crucial. MMP12 is a potential oncogene that is significantly overexpressed in numerous tumor types, including colon adenocarcinoma, liver hepatocellular carcinoma, CESC, and breast invasive carcinoma [14–17]. Particularly in squamous cell carcinoma, its expression is significantly increased, such as in esophageal and oral squamous cell carcinomas [18–19]. This study used data collected from TCGA

datasets to analyze MMP12 levels in CESC. MMP12 was significantly overexpressed in many cancer types. Moreover, a significant difference in MMP12 expression was detected between CESC and healthy cervical cells or tissue samples. ROC curve analysis also revealed that MMP12 levels in CESC exhibited a high degree of diagnostic uncertainty, and MMP12 expression effectively discriminated between patients with CESC and healthy individuals. Therefore, MMP12 expression is a promising biomarker for the diagnosis of cervical cancer.

Tumor surroundings influence tumor progression, and crosstalk between tumor cells and their surrounding environment plays an essential role in tumor development, invasion, and treatment efficacy [20–21]. The tumor microenvironment is a defining feature of most lethal solid cancers [22]. For example, the inactivated bacterium *Prevotella intermedia* accelerates the development of oral squamous cell carcinoma by suppressing tumor-suppressing genes and altering the tumor microenvironment [23]. DNA methylation, which can reduce gene expression, profoundly integrates into the tumor microenvironment [24]. This study explored the mechanism underlying high MMP12 expression in CESC and found that MMP12 elevation may be associated with DNA hypomethylation of MMP12. Patients with hypomethylated MMP12 exhibited a poorer prognosis than those with hypermethylated MMP12.

5. Conclusions

The findings of this research provide evidence that the detection of MMP12 is linked to a poorer outcome in CESC. Therefore, MMP12 may be a promising new biomarker for predicting the outcomes of cervical malignancy, which has important implications for understanding the evasion mechanisms of the tumor and the potential for immune-based therapies. In conclusion, the study provides new evidence highlighting the importance of MMP12 as a biomarker for forecasting the outcome of CESC and its potential as a therapeutic target. These findings will significantly contribute to the field of CESC oncology and offer new avenues for clinical research and treatment. However, the distinct mechanism responsible for the effect of MMP12 on the onset and progression of CESC has not been fully elucidated. Therefore, additional research is necessary to elucidate the complex biological pathways through which MMP12 functions. Future research should broaden the dataset to include a larger and more diverse population of patients with CESC. In addition, incorporating detailed clinical data, including chemotherapy regimens, may provide a more thorough understanding of the correlation between MMP12 expression and prognosis. Therefore, experimental validation is necessary to corroborate the findings of this study.

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Disclosure statement

The authors declare no conflict of interest.

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