

Bioinformatics Analysis Reveals that Minichromosome Maintenance 10 Replication Initiation Factor Is a Possible Prognostic Marker for Patients With Adrenocortical Carcinoma

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Abstract

Background/Aim: Adrenocortical carcinoma (ACC) is a rare but highly malignant endocrine tumor arising from the adrenal cortex, with a 5-year survival rate of less than 40%. Identifying prognostic biomarkers and therapeutic molecular targets is essential to improve the survival rate of ACC patients. Minichromosome maintenance protein 10 (MCM10) is known to play a role in DNA replication, and recently, the relationship between *MCM10* expression and the prognosis of various cancers has been reported. However, the expression levels of *MCM10* mRNA in ACC tissues and the relationship between MCM10 expression and prognosis of ACC patients have not yet been reported.

Materials and Methods: MCM10 mRNA expression and survival in ACC patients were analyzed using the TCGA database with UALCAN and GEPIA platforms, assessing *MCM10* mRNA expression across disease stages and its correlation with patient survival.

Results: *MCM10* was found to be significantly overexpressed in ACC tissue from stage IV patients compared to stage I and II patients ($p < 0.001$), and elevated *MCM10* expression correlated with poorer prognosis in ACC patients ($p < 0.001$).

Conclusion: These findings suggest that *MCM10* may be a potential prognostic biomarker for ACC and may provide new insights into its role in tumor biology. Further studies are needed to elucidate the therapeutic significance of *MCM10* and its mechanistic involvement in ACC progression.

Keywords: MCM10, adrenocortical carcinoma, Kaplan–Meier survival plot, prognosis.

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Introduction

Adrenocortical carcinoma (ACC) is a tumor originating from the adrenal cortex. It is one of the rarest cancers, with an estimated annual incidence of 0.5-2.0 cases per million. The majority of patients are under 5 years of age and between 40 and 50 years of age (1). The prognosis for this cancer is poor, with a 5-year survival rate of 38.6% and a median survival time of 31.9 months after tumor resection (2). Furthermore, if the patients have metastatic disease, the 5-year survival rate is less than 15% (3). Therefore, selecting appropriate prognostic biomarkers is important for treating patients with ACC, but currently, no clinically useful prognostic biomarkers exist for ACC.

Minichromosome maintenance protein 10 (MCM10) is an evolutionarily conserved protein required for DNA replication in eukaryotes. It is an essential replication factor that plays a key role in maintaining the integrity of DNA replication forks (4). MCM10 is essential for promoting cell proliferation and is overexpressed in many malignant tumors. Correlation between the level of MCM10 expression and prognosis has been reported in many cancers, suggesting its role in tumor initiation and progression (5-13). However, the relationship between *MCM10* expression and prognosis in ACC has not yet been investigated. Because ACC is one of the tumors with a very poor prognosis, it is of great importance to determine whether the expression of *MCM10* in ACC tissues is high or low and whether high expression correlates with poor prognosis.

To investigate whether *MCM10* can be a prognostic factor for ACC, comprehensive analysis of mRNA expression in ACC tissues from as many ACC patients as possible and information on clinical prognosis are needed. However, it is difficult for a single clinical institution to build a database that meets these criteria. However, publicly available databases are now available. The Cancer Genome Atlas (TCGA) is a cancer genome information program containing information on over 20,000 primary cancer and normal tissue samples from 33 cancer types (14). Two platforms for analyzing this database, UALCAN and GEPIA, are freely available. UALCAN is a cancer data

analysis platform that uses TCGA data to evaluate gene expression and its impact on patient survival in 33 cancer types (15). GEPIA is also a cancer data analysis platform that provides profiling plots and patient survival analysis functions (16). We previously used UALCAN and GEPIA to reveal the expression and prognostic value of *DDX39* (17) and *stathmin 1* (18) in ACC patients from the TCGA database. Similarly, using UALCAN and GEPIA, we have shown that *DDX39* and *STC-1* are genes associated with the prognosis of uveal melanoma (19, 20), that *ANLN* is a gene associated with the prognosis of pancreatic cancer (21), and that overexpression of *DDX39* in tumor tissues is associated with shorter survival times in patients with clear cell renal carcinoma and papillary cell renal carcinoma (22).

In present study, we conducted *in silico* analysis using two platforms, UALCAN and GEPIA, to investigate the relationship between *MCM10* mRNA expression profiles in ACC tissues from the TCGA database and the prognosis of ACC patients.

Materials and Methods

Evaluation of MCM10 expression in tumor tissues from patients with adrenocortical carcinoma. The gene name “MCM10” was registered in the TCGA database. The expression levels of *MCM10* mRNA in tumor tissues from patients with adrenocortical carcinoma (ACC) of various stages registered in the TCGA database were investigated using the UALCAN platform [stage 1 (n=9), stage 2 (n=37), stage 3 (n=16), stage 4 (n=15)] (23) and GEPIA platform [ACC tissues (n=77) vs. normal adrenocortical tissues (n=128)] (24).

Survival analysis according to MCM10 mRNA expression levels in adrenocortical carcinoma tissues. To investigate the impact of *MCM10* expression levels in ACC on patient survival, survival analysis was performed using the UALCAN platform. The gene name “MCM10” was entered into the TCGA database, median cutoff values were selected, and Kaplan-Meier curves of ACC patients were

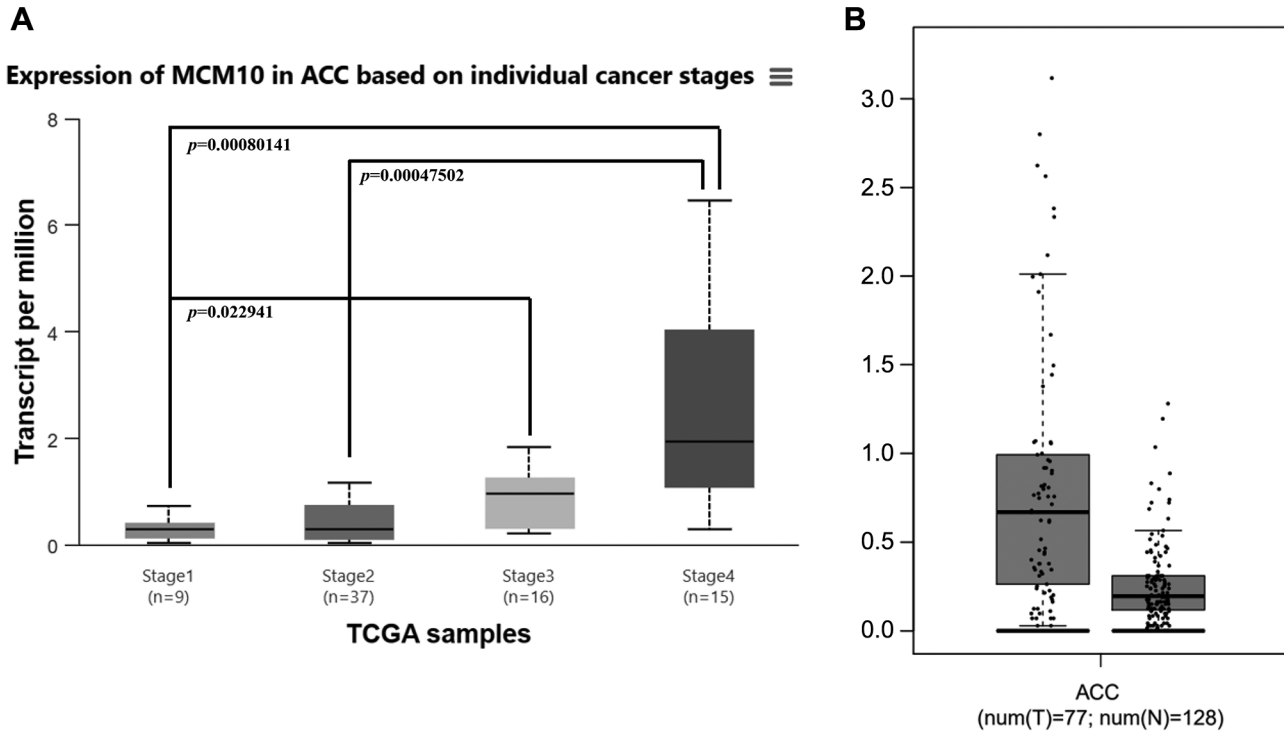


Figure 1. mRNA expression analysis *MCM10* for adrenocortical carcinoma tissues from TCGA database. (A) The boxplots were downloaded from the University of Alabama at Birmingham CANcer data analysis Portal (UALCAN) based on The Cancer Genome Atlas (TCGA) adrenocortical carcinoma (ACC) dataset. Expression of *MCM10* mRNA in ACC tissues is analyzed according to individual cancer stages, Stage I (n=9), Stage II (n=37), Stage III (n=16), Stage IV (n=15). (B) The boxplots were downloaded from the Gene Expression Profiling Interactive Analysis (GEPIA) based on TCGA ACC dataset. The right box represents expression levels of *MCM10* mRNA normal adrenal cortex tissues (n=128), wherein the left box represents ACC tissues (n=77). *MCM10*: Minichromosome maintenance 10 replication initiation factor.

generated. Furthermore, the bioinformatics platform GEPIA was used to investigate the impact of *MCM10* mRNA expression levels on overall survival and disease-free survival of ACC patients, and a p -value <0.05 considered statistically significant.

Results

mRNA expression of MCM10 was increased in adrenocortical carcinoma tissues of stage IV patients compared to stage I and II patients. We analyzed the TCGA dataset using the UALCAN platform to determine whether the increased *MCM10* mRNA expression levels in ACC tissues depended on the ACC stage. Figure 1A shows a graph of *MCM10* mRNA expression in ACC based on individual tumor stage (I, II, III, IV, n=9, 37, 16, 15, respectively). The mRNA levels

of *MCM10* were significantly higher in tumor tissues from stage IV patients compared with stage I and II patients ($p=0.00080141$ and $p=0.00047502$, respectively). Furthermore, we simply examined the expression levels of *MCM10* mRNA in normal adrenal cortex tissues (n=128) and ACC tissues (n=77) using the GEPIA platform and found that the expression levels of *DTL* mRNA were higher in ACC tissues than in normal tissues.

High levels of MCM10 mRNA expression correlate with shorter survival in patients with adrenocortical carcinoma. Using the UALCAN platform, Kaplan-Meier survival curves were generated for patients with ACC tissues with high (n=20) and low/moderate (n=59) *MCM10* expression levels. The results showed that increased mRNA expression levels of *MCM10* correlated with shorter patient survival

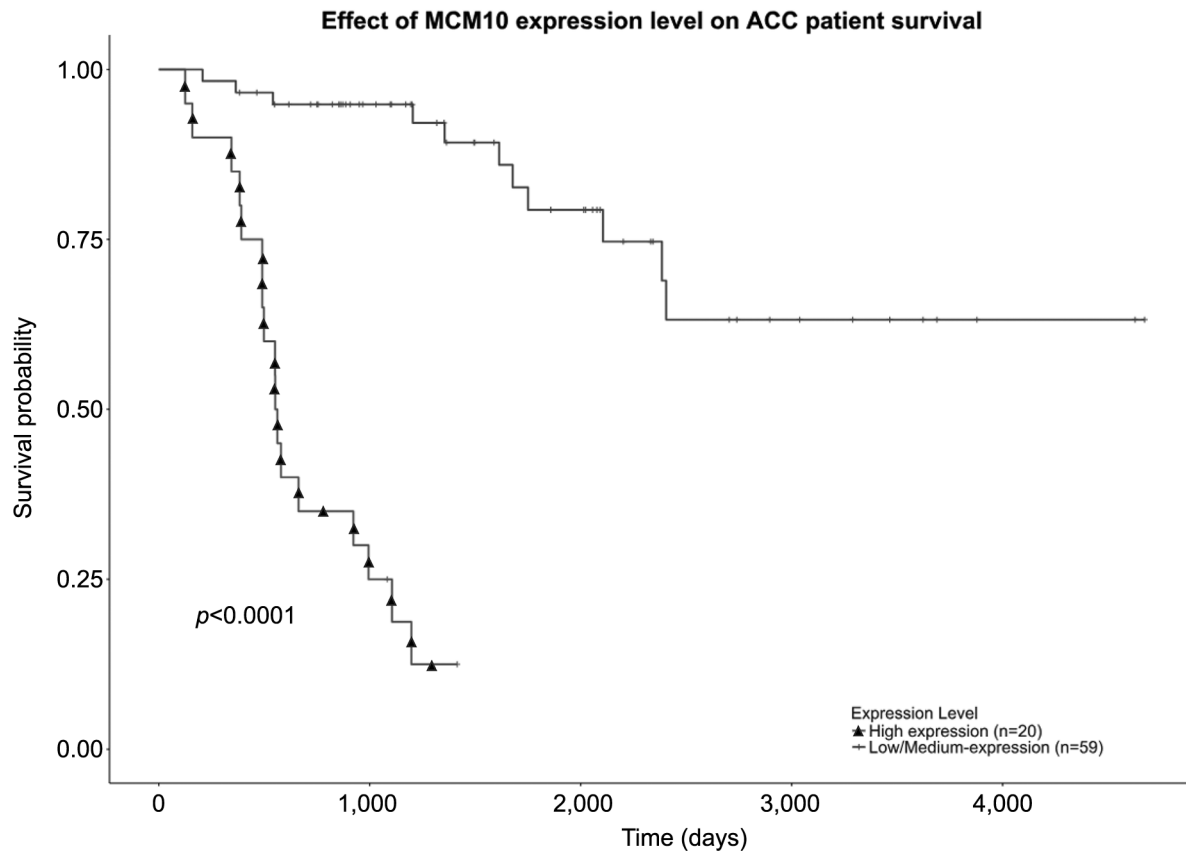


Figure 2. Kaplan-Meier survival plots for adrenocortical carcinoma patients with high and low/medium levels of *MCM10*. Using the University of Alabama at Birmingham Cancer Data Analysis Portal (UALCAN) platform, we analyzed overall survival rates in patients with adrenocortical carcinoma (ACC) based on *MCM10* expression levels. The survival curves for ACC patients were compared between those with high *MCM10* expression ($\blacktriangle$, $n=20$) and those with low/medium *MCM10* expression ($n=59$). $p<0.05$ was regarded as statistically significant. *MCM10*: Minichromosome maintenance 10 replication initiation factor.

($p<0.0001$) (Figure 2). Furthermore, we used the GEPIA platform to generate Kaplan-Meier survival curves to analyze overall survival and disease-free status in patients with ACC tissues with high ($n=38$) and low ($n=38$) *MCM10* mRNA expression. We found that increased expression levels of *MCM10* correlated with shorter overall patient survival ($p=0.00000011$) (Figure 3A) and shorter disease-free survival ($p=0.00053$) (Figure 3B).

Discussion

In present study, we used the bioinformatics platforms GEPIA and UALCAN to analyze *MCM10* mRNA expression and Kaplan-Meier survival in patients with ACC. The

results showed that the expression level of *MCM10* mRNA was significantly increased in ACC tissues from stage IV patients compared with stage I and II ACC patients. Furthermore, we found that increased expression of *MCM10* mRNA correlated with shorter overall and disease-free survival in patients with ACC.

Because the expression of *MCM10* mRNA in ACC tissues from stage IV patients is much higher than that of stage I and II patients, we investigated the literature reporting strong expression of *MCM10* in cancer tissues compared with normal tissues. As a result, it has been reported that *MCM10* mRNA is highly expressed in many types of cancer tissues including uterine corpus endometrial carcinoma tissues (5), cervical cancer tissues (6), lung squamous cell carcinoma

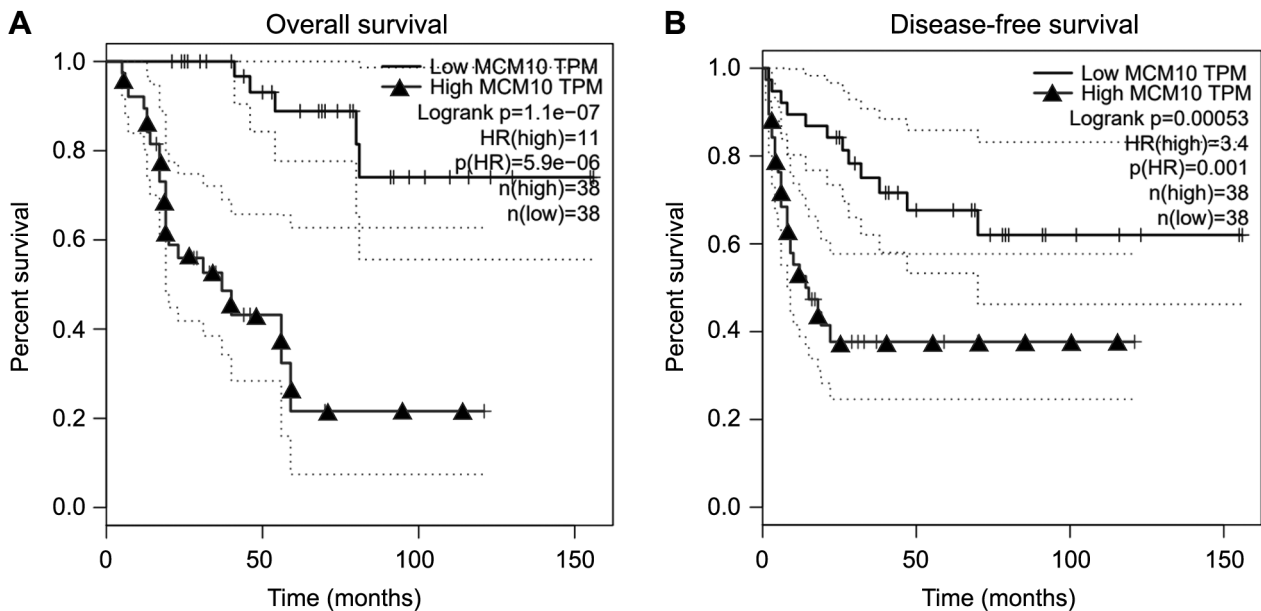


Figure 3. Kaplan-Meier graph of overall survival and disease-free survival in patients with adrenocortical carcinoma with high and low levels of MCM10. (A) The Gene Expression Profiling Interactive Analysis (GEPIA) platform was used to perform overall survival analysis and (B) disease-free survival analysis based on MCM10 mRNA expression. The overall survival curves and disease-free survival curves of patients with adrenocortical carcinoma were compared between the high MCM10 expression group ($\blacktriangle$, $n=38$) and the low MCM10 expression group ($n=38$). $p<0.05$ was regarded as statistically significant. MCM10: Minichromosome maintenance 10 replication initiation factor.

tissues (7), glioma tissues (8), ovarian cancer tissues (9), esophageal cancer tissues (10), hepatocellular carcinoma tissues (11), breast cancer tissues (12), medulloblastoma tissues (13) compared with normal tissues.

Furthermore, a search for literature that mentioned the relationship between high MCM10 expression and poor prognosis revealed that the higher the MCM10 expression, the worse the prognosis in triple-negative breast cancer (TNBC), uterine corpus endometrial carcinoma (UCEC), glioma, ovarian cancer, esophageal cancer, hepatocellular carcinoma (HCC), lung cancer, and urinary tract cancer. Huang *et al.* reported that class I TNBC, a subtype of TNBC for which MCM10 is a useful biomarker, may have a worse prognosis than class II TNBC, for which phosphatidylinositol-3,4,5-trisphosphate dependent rac exchange factor 2 (PREX2) serves as a biomarker (25). Chen *et al.* reported that MCM10 is mutated and overexpressed in UCEC tissues and is involved in DNA replication, cell cycle, and DNA repair, and that silencing MCM10 significantly inhibits UCEC cell proliferation *in vitro* (5). Tian *et al.*

reported that MCM10 is highly expressed in glioma tissues and that MCM10 expression is an independent prognostic factor for glioma patients. They also reported that MCM10 may be related to drug resistance and glioma development (26). Furthermore, Wu *et al.* evaluated the relationship between MCM10 expression and the prognosis of patients with ovarian cancer and showed that MCM10 is highly expressed in ovarian cancer tissues and that increased MCM10 expression is significantly associated with decreased overall survival (9). Wan *et al.* showed that key genes in the MCM family, including MCM10, were significantly correlated with the overall survival rate of HCC patients, and that MCM10 expression was significantly elevated in HCC cell lines. They also showed that knockdown of MCM10 significantly suppressed cell proliferation and increased caspase-3 activity in HCC cells. These findings suggest that MCM10 may be a predictor of poor prognosis in HCC patients and may act as a molecule that promotes HCC cell progression (11). Wang *et al.* found that high MCM10 expression was significantly associated

with early and late recurrence, pathological stage, and poor overall survival of lung cancer patients (27). Li *et al.* demonstrated *in vitro* that knockdown of the *MCM10* gene significantly suppressed cell proliferation in two urothelial carcinoma cell lines and that overexpression of *MCM10* was associated with a poor prognosis in patients with urothelial carcinoma (28).

Although it may depend on the type of cancer, it is necessary to clarify how MCM10 acts in cancer tissue to worsen prognosis. Overexpression of MCM10 is involved in DNA replication, the cell cycle, and DNA repair. Suppression of MCM10 expression significantly inhibits the proliferation of UCEC, HCC, and urothelial carcinoma cells and increases caspase-3 activity in HCC cells. This suggests that high expression of MCM10 may promote cancer cell proliferation and suppress apoptosis. Furthermore, Tian *et al.* suggested that abnormal over-expression of *MCM10* induces DNA over-replication and genomic instability, promoting the proliferation and metastatic ability of esophageal cancer cells *in vitro* and *in vivo*, not only promoting proliferation and survival but also inducing genomic instability in cancer cells and promoting malignant progression (10). Wu *et al.* reported that silencing *MCM10* suppressed the proliferation, invasion, migration, and epithelial-mesenchymal transition of colorectal cancer cells. Furthermore, this silencing induced G1/S cell cycle arrest and apoptosis through activation of the p53/p21 pathway and downregulation of CCND1. These findings suggest that MCM10 may promote the malignant progression of colorectal cancer by inhibiting the tumor suppressor p53/p21/CCND1 pathway (29).

To date, there have been no reports on the degree of *MCM10* expression in ACC tissues and the relationship between *MCM10* expression levels and the prognosis of ACC patients. However, it is quite possible that MCM10 promotes the malignant transformation of ACC cells.

Conflicts of Interest

The Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

All authors contributed to the conception and design of the study. Data collection and analysis were performed by Shin-nosuke Yamashita, Yoshiatsu Tanaka, Shajedul Islam and Yasuhiro Kuramitsu. Shin-nosuke Yamashita and Yoshiatsu Tanaka wrote the first draft of the manuscript, Takao Kitagawa and Yasuhiro Kuramitsu commented on an earlier version of the manuscript. All Authors read and approved the final manuscript.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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