

# High Expression of Complement Component C7 Indicates Poor Prognosis of Endometrial Cancer and poor 5-year OS

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## Research Article

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# Abstract

**Background:** Corpus Carcinoma is the most commonly diagnosed female cancer worldwide. However, the well-known biomarkers are not enough to meet the needs of precision medicine. Novel targets are desirable and highly valuable for improved patient survival. In this regard, we identified complement component C7 as one of the candidates based on data from the TCGA database.

**Method:** C7 expression was examined by mRNA expression profile in 425 cases of corpus carcinoma, including grade 3 data (such as mRNA-seq, miRNA-seq, and clinical data) from 406 primary corpus carcinoma tissues and 19 normal controls from the dataset. The availability of data is demonstrated by heat maps, and the distribution of genes is demonstrated by volcanic maps. Then the value of C7 was demonstrated on the basis of genomics and clinical epidemiology respectively, confirmed by grade 3 data from TCGA. The relationship between the C7 expression and five-year survival of corpus carcinoma patients was analyzed in order to investigate the function of C7 in corpus carcinoma.

**Result:** In our present study, we reported for the first time that C7 was an independent prognostic factor of corpus carcinoma and the 5-year survival rate of patients with high C7 expression is lower than that of patients with low C7 expressions. ( $p=0.02265$ )

**Conclusion:** In summary, high expression of C7 may promote corpus carcinoma development. Our present study laid a foundation to help clinicians improve the identification of patients for C7 in the era of precision medicine.

## Introduction

Corpus carcinoma is the most common gynecological malignant tumor and the fourth most common malignant tumor after breast cancer, colorectal cancer, and lung cancer in women in developed countries. According to the American Cancer Society, there are expected to be 66,570 new diagnoses and 12,940 deaths in 2021(1). The existing cancer markers, such as serum CA125 and CA199, are not enough to meet the needs of precision medicine. Therefore, new biomarkers are needed to accurately diagnose corpus carcinoma.

The complement system is an essential part of the innate immune system, in which many proteins work in a cascade, forming a complex pore structure. Complement proteins in plasma are mainly synthesized in hepatocytes, but also secreted by endothelial cells, leukocytes and epithelial cells.(2–5).In extravascular tissues, complement proteins are also involved in intercellular communication, organ regeneration, Angiogenesis, epithelial-mesenchymal transformation, and cell migration. Markiewski et Al showed that regulatory t cells (Tregs) in breast tumors can be activated by C5a receptor protein in the tumor microenvironment, which is a component of the classical complement cascade (5). In addition, peptide antagonists of C5a receptor can enhance the anti-tumor response of CD8 T cells, which is as effective as Taxol in delaying tumor growth.

C7 belongs to the complement system, which is composed of natural complement, complement controlling component and complement receptor. It is an important part of the natural immune system and plays a vital role in the coordination of natural immune and adaptive immune responses, c7 is a 93-kDa serum glycoprotein encoded by the C7 gene. C7 and other terminal complement components (C5B, C6, C8 and C9) membrane attack form complex (Mac), which functions complement the lethality unit system(6). The insertion of C7 into the cell membrane was identified as a key step in the formation of MAC (Membrane Attack by Complement, MAC) (7).

C7 has been involved in the development of several malignancies in previous studies. It has been reported that the expression of C7 is increased in normal human tissues, but significantly decreased in human esophageal, colon and kidney cancer tissues (8). In addition, the expression of C7mRNA decreased gradually in normal, benign, borderline and malignant ovarian tissues, and there was a negative correlation between C7 expression and tumor grade in patients with ovarian cancer(9). Meanwhile, some researchers believe that C7 can promote the progression of cancer. The expression of C7 was up-regulated in ovarian cancer, while knockout of C7 gene decreased the proliferation of ovarian cancer cells(10). The significant up-regulation of C7 protein is also a necessary condition for maintaining the dryness of stem cells in liver tumor initiation cells(11).

C7 has recently been shown to be associated with the prognosis of patients with prostate cancer and to be a novel prognostic biomarker and immunotherapeutic target for prostate cancer(12). In addition, C7 is an independent prognostic factor for breast cancer, and patients with high C7 expression are not susceptible to Te (taxane and anthracyclines)-based chemotherapy(13).

Until now, the role of C7 in human corpus carcinoma was

unknown. In this study, we firstly identified C7 was an independent prognostic factor of corpus carcinoma and its expression was significantly higher in lower 5-year survival patients compared with higher 5-year survival patients. By mRNA expression analysis of a large population of 406 cases, we provided the first clinical evidence that a high expression of C7 promoted breast cancer progression.

## **Material And Methods**

### **Data collection**

First, from the Cancer Genome Atlas (TCGA) (<https://genomecancer.ucsc.edu/>) to retrieve the TCGA -UCEC samples (Uterine corpus endometrial carcinoma) mRNA expression patterns. This included retrieval of grade 3 data (mRNA-seq, miRNA-seq, and clinical data) from 406 primary endometrial adenocarcinoma tissues and 19 normal controls from the dataset.

The downloaded original data were open data, analyzed by transcriptome atlas, and the experimental method was transcriptome sequencing technology with quantitative expression.

### **Data pre-processing**

Taking the correction  $p < 0.05$  and  $\log_2$  (multiple change)  $< 1$  as the threshold, the original counting data are normalized by the Edger software package in R language, and the differentially expressed genes in normal control and liver cancer tissues are screened. The volcanic map and heat map are used to further evaluate the quality of the data, make sure that the data quality meets the standard, and proceed to the next step.

Then the clinical data in TCGA database were used to combine gene expression and survival interval. Combining this table with the corrected gene expression values, the survival package of R and Cox analysis were used to compare the 5-year survival rate of patients with high and low expression of the expressed genes and to calculate the P value. Single Gene C7 was screened out,  $p = 0.02265$ , which has significance in gene statistics and clinic.

## Result

### The heatmap

The image (figure 1) shows the corpus carcinoma data downloaded from the TCGA database compared to normal tissue. The red color indicates increased gene expression, while the green color indicates decreased gene expression. The brightness change of color indicates how much the amount of gene expression changes. The brighter the color, the more the amount of gene expression. The quality of heat map data can be used for further data analysis.

### The volcano map

The volcano map (figure 2) obtained from the data downloaded by TCGA. The red spot on the upside of the volcano map shows the genes expressed in corpus carcinoma that are significantly higher than those in normal tissues ( $p < 0.05$ ), on the downside, the gene in corpus carcinoma was significantly lower than that in normal tissue ( $p < 0.05$ ). The black-in-the-middle region showed no significant difference in gene expression between corpus carcinoma and normal tissue ( $p > 0.05$ ).

### The survival curve

In the survival curve (Figure3), high expression and low expression of C7 gene had a significant effect on the survival rate of patients with high expression and low expression of C7 gene, indicating that the five-year survival rate of patients with high expression and low expression of C7 gene was significantly different from that of patients with high expression and low expression of C7 gene.

### Statistical Methods:

Genetic analysis of UCEC samples from TCGA dataset updated on 21 September 2021 was performed using R (version 4.0.5, R Foundation, Vienna, Austria) and the samples were determined to be statistically significant. Under the premise of ( $FDR < 0.05 \& \log FC > 2$ ,  $FDR < 0.05 \& \log FC < -2$ ), genes with

statistical significance were combined with the five-year survival of patients in the database respectively, and COX regression model was used to obtain k-M curves of high and low expression of C7 gene

## Discussion

Our study investigated the prognostic and gene effects of C7 in corpus carcinoma for the first time. Patients with lower C7 expression has longer five-year survival than those with higher C7 expression, a high expression of C7 indicated a poor prognosis of patients. Moreover, C7 was an independent prognosis factor. These findings indicated that C7 may serve as a tumor promoter, consistent with the study by Zhang about the role of C7 in corpus carcinoma, C7 promotes breast cancer progression by activating the VEGF, MAPK, or JAK stat signaling pathways(13), but further in vitro and in vivo studies are needed to confirm these findings.

However, C7 has a limited role in tumor progression. A variety of studies indicated that the membrane attack complex, including C5b, C6, C7, C8, C9, could trigger the activation of several tumorigenesis signal transduction pathways, including the PKC signaling, MAPK family, Ras/Raf/ERK1 pathway and Gi protein/PI3K/Akt pathway(14, 15). Besides, C5b-9 also involved in cell cycle activation, accomplished by affecting and regulators, such as CDK2,CDK4, p21, cyclin D1 PCNA and CDC2 ,as well as main cell cycle kinases(16, 17). In addition, C5b-9 had an antiapoptotic effect by adjusting the phosphorylation of Bad and FOXO1, and suppressing the activation of NF-kB, caspase-8 and Bid(18-20). In this situation, other components should also be detected, in order to provide a more reliable mechanism to reveal the roles of the complement in corpus carcinoma progression.

## Conclusions

Taken together, our study showed the first evidence that C7 expression was an independent prognosis factor in corpus carcinoma patients. High expression of C7 indicated poor prognosis. The findings highlight the importance of C7 in corpus carcinoma progression and lay a foundation to help clinicians improve the identification of patients by C7 in the era of precision medicine.

## Declarations

### DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

### FUNDING

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The authors declare no conflicts of interest.

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## Figures

### Figure 1

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# Volcano

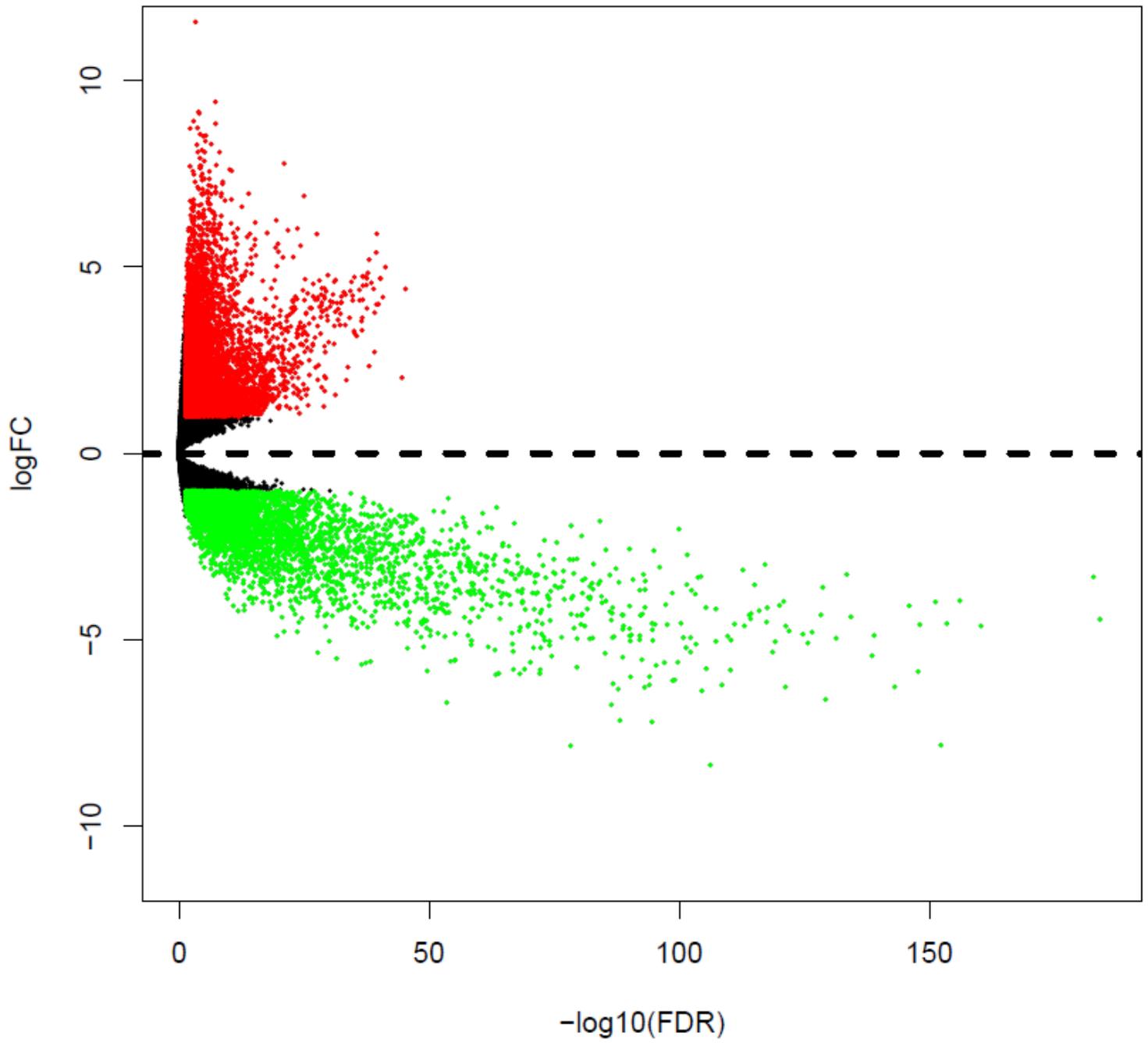


Figure 2

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surival curve (p=0.02265)

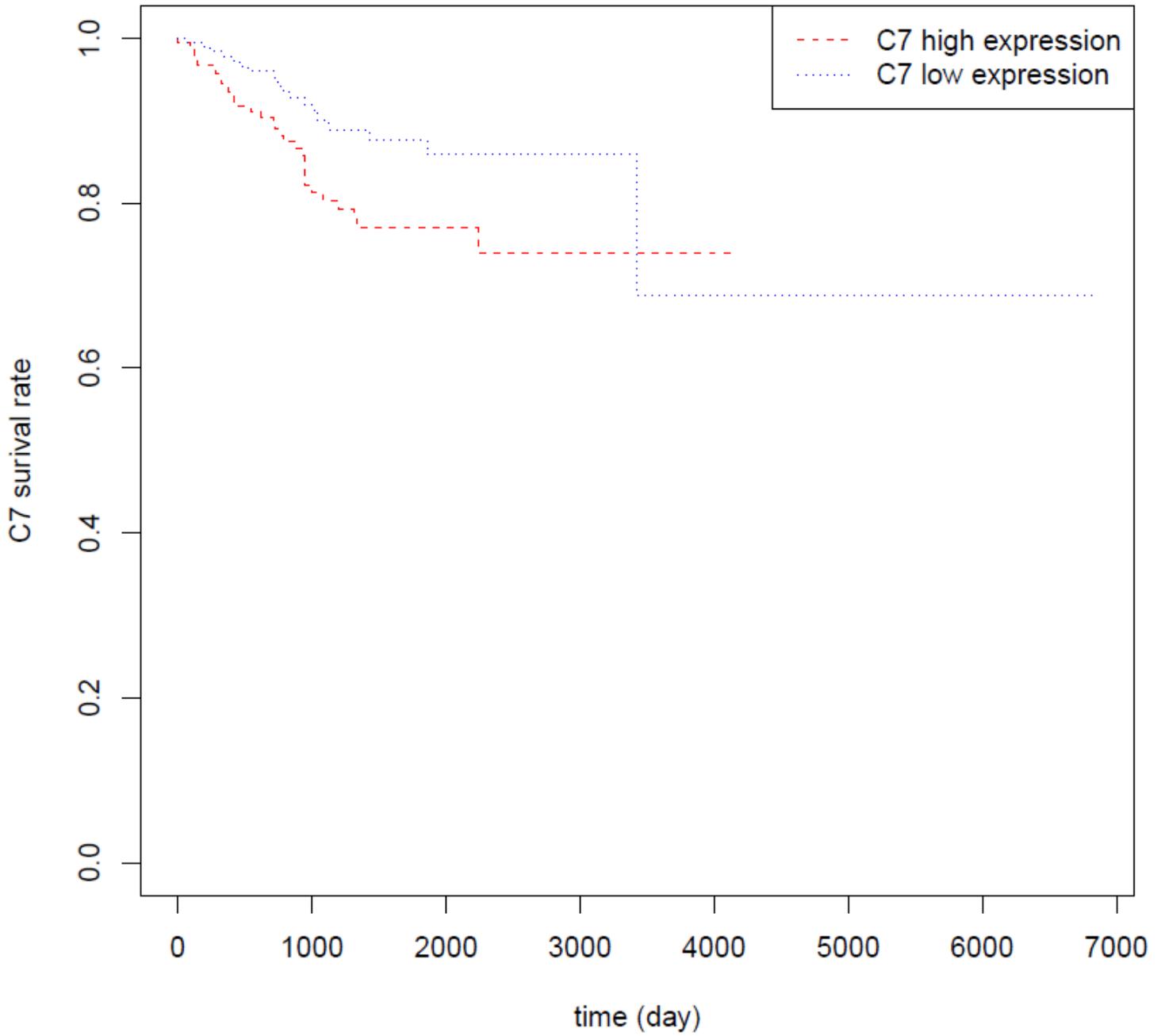


Figure 3

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