EccDNA-oriented *ITGB7* expression in breast cancer

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Background: Extrachromosomal circular DNA (eccDNA) is omnipresent in cancers and related to the progression of tumors and oncogene amplification. However, its function in breast cancer (BC) is unclear.

Methods: After constructing the DNA library, CLeavage Effects by Circularization for *In vitro* Reporting of sequencing was performed for eccDNA detection using 1 BC tissue sample. Fastqc was used to evaluate the quality of the original data. Burrows-Wheeler-Alignment Tool was used to compare the original data to the reference genome. A Circle-MAP was subsequently performed to detect eccDNA, and Bedtools was used to annotate the eccDNA genes. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were conducted by ClusterProfiler. The Genotype-Tissue Expression and the Cancer Genome Atlas databases were used to collect the ribonucleic acid–sequencing data of the BC and normal samples. A Gene Expression Profiling Interactive Analysis, the University of Alabama at Birmingham CANcer data analysis Portal, and Kaplan-Meier survival curves were used to analyze the Cancer Genome Atlas data.

Results: A total of 200 eccDNA genes, including *IGTB7*, were obtained. About the biological processes (BPs), these 200 genes were mainly enriched in actin cytoskeleton reorganization and axon guidance. Concerning the molecular functions (MFs), these 200 genes were mainly enriched in sodium ion transmembrane transporter activity and metal ion transmembrane transporter activity. As for cellular components (CCs), these 200 genes were mainly enriched in the transcription regulator complex and focal adhesion. *ITGB7* was significantly enriched in cell-matrix adhesion and localization within the membrane in the BPs, integrin binding in the MFs, and cell-substrate junction and focal adhesion in the CCs. The 200 eccDNA genes were mainly enriched in the PI3K-Akt signaling pathway and focal adhesion. Notably, *ITGB7* was enriched in focal adhesion, ECM-receptor interaction, the PI3K-Akt signaling pathway, and human papillomavirus infection. Besides, *ITGB7* was significantly upregulated in BC patients and was associated with the menopause status of the BC patients.

Conclusions: *ITGB7* might serve as a prognostic marker for BC patients. *ITGB7* has important implications for the individualized clinical treatment of BC patients.

Keywords: Extrachromosomal circular DNA (eccDNA); breast cancer (BC); *ITGB7*; prognosis; functional enrichment analyses

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Introduction

Breast cancer (BC), which is considered a systemic disease with inter- and intra- tumoral heterogeneity, has a poor prognosis (1). It remains the most frequently diagnosed malignancy and the leading cause of malignancy-related deaths among women worldwide (2,3). It was reported that there were approximately 2.26 million new cases of BC in 2021, which accounts for 11.7% of the total new cases of cancer worldwide and contributes significantly to the disease burden (4).

Early BC is potentially curable, but advanced BC is typically aggressive and difficult to treat (5-7). Despite many advanced strategies for treating BC, including surgery, chemotherapy, endocrine therapy, and targeted therapy, recurrence and drug resistance inevitably occur in the treatment process, reducing the survival rate of BC patients. The prognosis of patients with distal metastasis remains poor. Many BC survivors experience lasting treatment-related side effects, have a severely reduced quality of life, and face an increased social burden (8). However, there are very few validated therapeutic targets and prognostic clinical biomarkers for BC (5). Thus, more sensitive and specific prognostic biomarkers for BC urgently need to be identified to provide opportunities to advance the targeted immunotherapy of BC.

Extrachromosomal circular DNA (eccDNA), characterized by a closed circular structure, are derived from repetitive genomic sequences like telomeric DNA or ribosomal sequences (9). EccDNA contains a large proportion of short direct repeats, indicating that microhomology-directed repair may involve in eccDNA formation (10). A wide distribution of eccDNA in different organisms and cells was identified by using genome sequencing, microscopic, and biochemical techniques. Till now, its biological function remains elusive. Some well-accepted functions of eccDNA are associated with genetic heterogeneity and evolution, genomic instability and plasticity, and environmental adaption mutation (11-14). Recently, it has been reported that eccDNA participates in tumorigenesis and tumor progression, and because of its important role in carrying oncogenes, promotes amplification of oncogenes and drug resistance genes (9,11,15,16). The functional mechanisms may relate to the random distribution of eccDNAs to daughter cells, the daughter cells may acquire a greater copy number of eccDNAs with a driving oncogene during each division, thus owning a proliferative advantage (17). A study has identified the presence of eccDNAs in BC (18), the distribution and function of eccDNAs, as well as the relationship between eccDNAs and clinical features in BC have not yet been explored.

Thus, based on data sets from the Genotype-Tissue Expression (GTEx) and the Cancer Genome Atlas (TCGA) databases and using CLeavage Effects by Circularization for In vitro Reporting of sequencing (Circle-seq), we analyzed the expression and function of all the eccDNA genes. The *ITGB7* was the only *ITGB* family gene found in the 200 eccDNA genes. *ITGB7* was enriched in focal adhesion, ECM-receptor interaction, the PI3K-Akt signaling pathway, and human papillomavirus infection. Additionally, *ITGB* was significantly upregulated in BC patients and associated with the characteristics of BC. It has been proven that ITGB7 may be the hub gene connecting glucose metabolism and cancer-specific immunity (19). Given its essential role, *ITGB7* could serve as a potential non-invasive biomarker for the prognosis of BC patients. We present the following article in accordance with the REMARK reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5716/rc).

Highlight box

Key findings

- *ITGB7* might serve as a prognostic marker and individualized clinical treatment target for BC patients.

What is known and what is new?

- Some studies have identified the presence of eccDNAs in BC.
- The distribution and function of eccDNAs, as well as the relationship between eccDNAs and clinical features in BC have not yet been explored. In this study, we identified the presence of *ITGB7* overexpression in BC, which is an important index for evaluating the prognosis of BC patients.

What is the implication, and what should change now?

- EccDNA-oriented ITGB7 can be considered as a prognostic marker for BC patients, as well as therapeutic targets.

Methods

Sample collection and data sources

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee at The Second Affiliated Hospital of Air Force Medical University (No. K202010-

04) and informed consent was taken from all the patients. All the diagnoses were confirmed by post-operative pathological examinations. The breast tumor tissue samples were collected from specimens obtained during surgery. The collected samples underwent subsequent Circle-seq analysis. The RNA-sequencing data of 9,736 tumor samples and 8,587 normal samples were downloaded from TCGA and GTEx databases, respectively, for the further TCGA analysis.

Library preparation for circle-seq

First, the purified high molecular weight DNA was obtained from the purified cells. After removing the linearized DNA by exonuclease, quantitative polymerase chain reaction was performed to confirm that linear DNA had been removed cleanly. Next, the eccDNA-enriched samples were used as the templates for the phi29 polymerase reactions, and the phi29-amplified DNA was sheared by sonication (Bioruptor). Finally, the purified fragmented DNA was used for the library construction. The library was purified by beads, and the size distributions of the fragments were analyzed.

EccDNA identification by circle-seq

The quality of the raw data was initially evaluated by Fastqc software, and the results included the base composition information of the sequence and the corresponding sequence quality information. The pair-end sequencing data were divided into 2 read files. Next, the Burrows-Wheeler-Alignment Tool was used to compare the reads to the reference genome, and Reads Mapping was employed to test the proportion of the uniquely mapped reads. Further, the Integrative Genomics Viewer was used to visualize the enrichment results of the reads in the gene set. In addition, Circle-Map software (https://github.com/iprada/Circle - Map) was used to detect eccDNAs and estimate the number of eccDNAs from the library. Finally, Bedtools was used to annotate the eccDNAs, and obtain the gene distribution results.

Enrichment analyses of extrachromosomal circular genes

The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology (GO) enrichment analyses of the selected eccDNA genes were conducted with ClusterProfiler of R software (version 3.6). The significant thresholds were as follows: a P value <0.05 and a count ≥1.

Expression profile of ITGB7 in pan-cancer

A Gene Expression Profiling Interactive Analysis (http://gepia2.cancer-pku.cn/) was conducted to investigate the expression of *ITGB7* in the pan-cancer samples compared to the corresponding normal samples. The results were visualized in dot plots.

Expression analysis of ITGB7 in BC

The University of ALabama at Birmingham CANcer data analysis Portal (UALCAN; http://ualcan.path.uab.edu/) online database was used to examine the status of *ITGB7* in the BC and normal samples, and to explore the correlations between expressions of *ITGB7* and the occurrence of BC. Additionally, the UALCAN database was further employed to determine the correlations between *ITGB7* expression levels and the pathological stages of BC patients.

Relationships between ITGB7 expressions and the prognosis of BC patients

The BC tumor samples from TCGA were first separated into high and low expression groups based on the median value of *ITGB7* expression. Kaplan-Meier Plotter (http://kmplot.com/analysis/) was used to investigate the correlations between the expression levels of ITGB7 and outcomes in BC patients, including overall survival (OS) and recurrence-free survival (RFS). Further, to investigate the effects of *ITGB7* expression on BC prognosis based on different clinical characteristics (i.e., pathological subtype, gender, menstrual status, and race), a Kaplan-Meier survival analysis was also conducted.

Statistical analysis

Statistical analysis was performed using SPSS software (IBM SPSS Statistics 21; SPSS Inc., Chicago, IL). All data were described as mean ± standard deviation (SD) if applicable. Statistical difference was performed with Student's *t*-test (two groups) or one-way ANOVA (three or more groups). The Kaplan-Meier method and log-rank test were used for survival analyses. P value <0.05 was considered statistical significance.

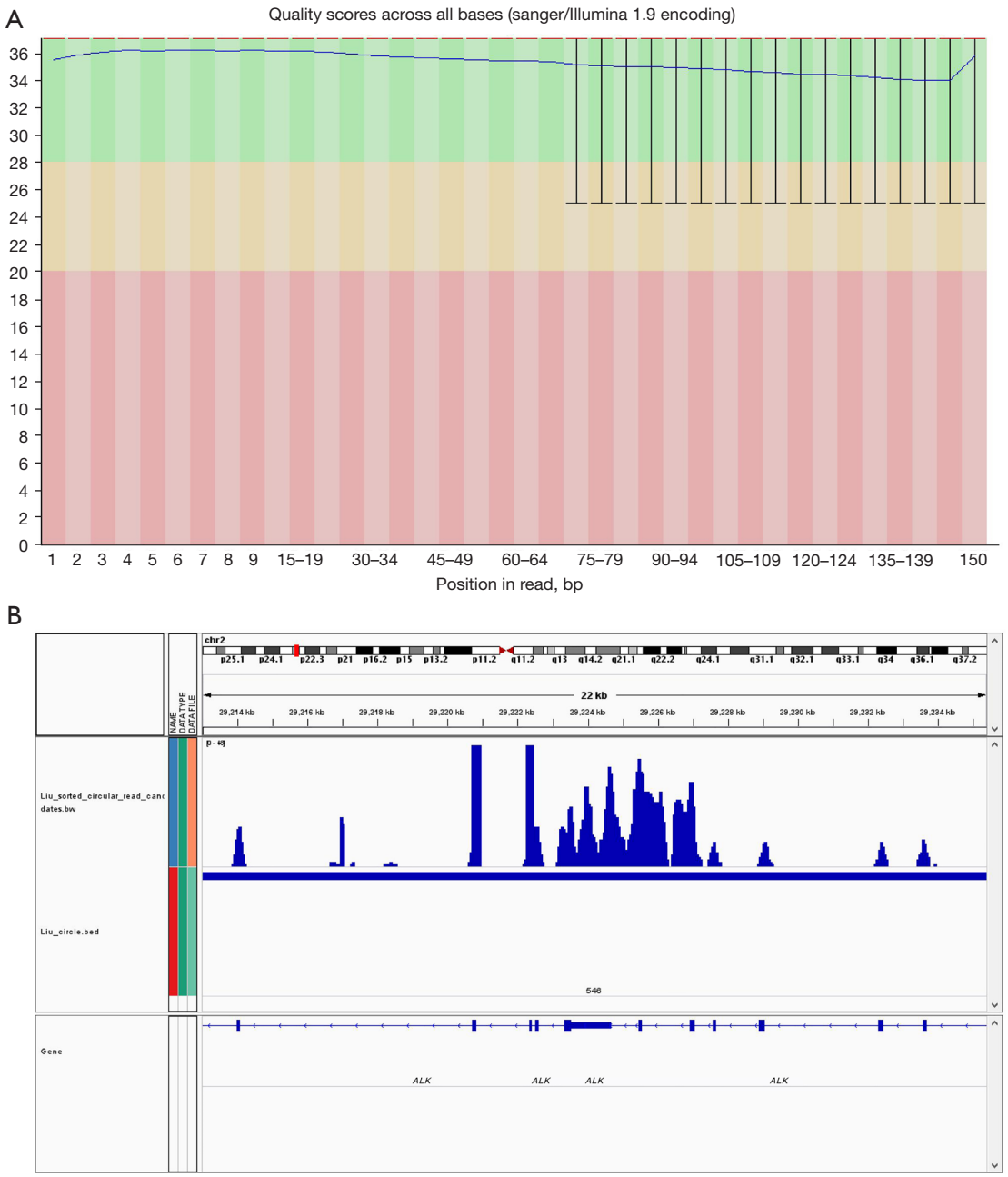

Figure 1 EccDNA identification by Circle-seq. (A) Fastqc. The y-axis is the mass score for each base; (B) Integrative Genomics Viewer. eccDNA, extrachromosomal circular DNA.

Results

EccDNA identification by circle-seq

The quality score of the per base sequence quality was around 36, implying that the quality of the sequencing data was good (*Figure 1A*). Moreover, the signal of the eccDNA reads on the *ALK* gene was obvious (*Figure 1B*).

Enrichment analysis of eccDNA

In relation to the biological processes (BPs), the enrichment analysis results of the 200 eccDNA genes revealed that

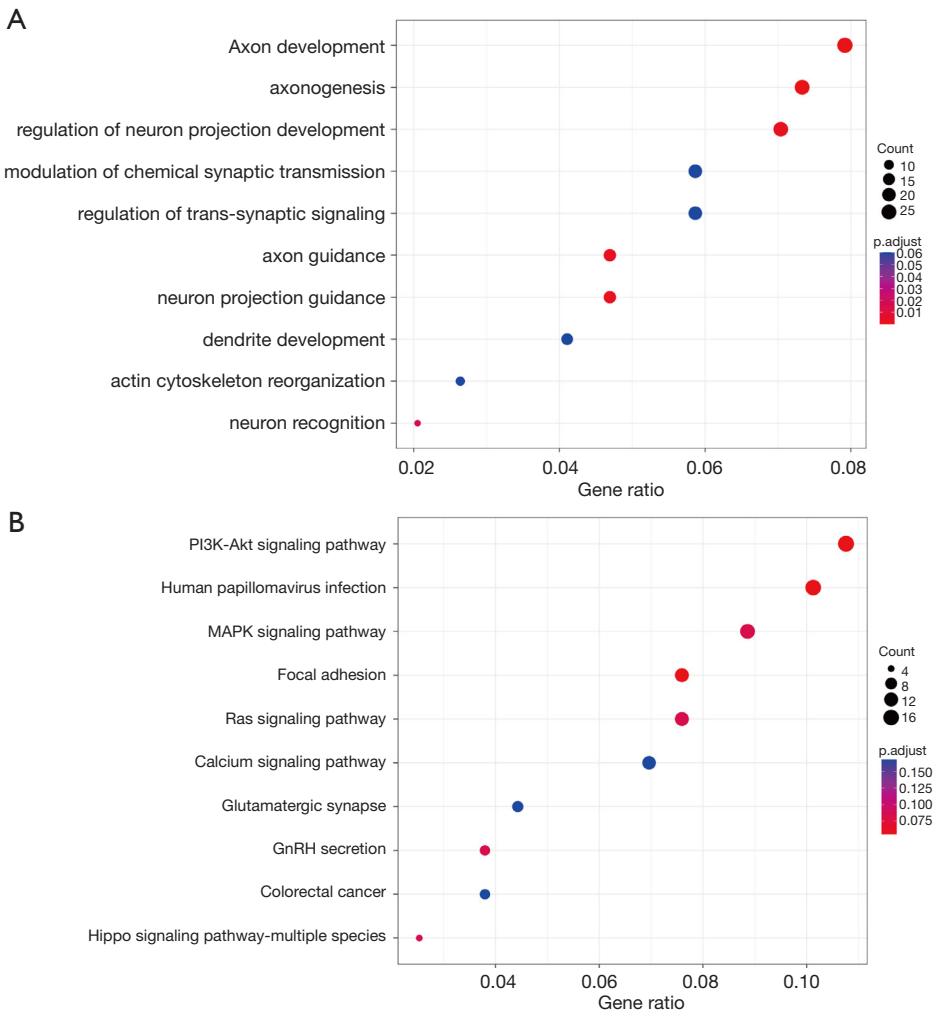

Figure 2 GO and KEGG pathway analyses of eccDNAs. (A) GO enrichment analysis; (B) KEGG enrichment analysis. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; eccDNA, extrachromosomal circular DNA.

actin cytoskeleton reorganization, axon guidance, neuron projection guidance, and axonogenesis were the major enriched terms. *ITGB7* was significantly enriched in cell-matrix adhesion and localization within the membrane in the BPs. In relation to the molecular functions (MFs), the 200 eccDNA genes were mainly enriched in activity and binding terms, such as sodium ion transmembrane transporter activity, metal ion transmembrane transporter activity, tubulin binding, and actin binding. *ITGB7* was only significantly enriched in integrin binding. In relation to the cellular components (CCs), transcription regulator complex, focal adhesion, and cell-substrate junction were the main enriched terms. *ITGB7* was significantly enriched in cell-substrate junction and focal adhesion (https://cdn.amegroups.cn/static/public/atm-22-5716-1.xls and *Figure 2A*). Additionally, the KEGG results demonstrated that the 200 eccDNA genes were mainly enriched in the PI3K-Akt signaling pathway, focal adhesion, Ras signaling pathway, and MAPK signaling pathway (https://cdn.amegroups.cn/static/public/atm-22-5716-2.xls, and *Figure 2B*). *ITGB7* was enriched in focal adhesion, ECM-receptor interaction, the PI3K-Akt signaling pathway, and human papillomavirus infection.

Expression profile of ITGB7 in pan-cancer

Compared to the normal samples, *ITGB7* was upregulated in 7 types of tumors, including cervical squamous cell

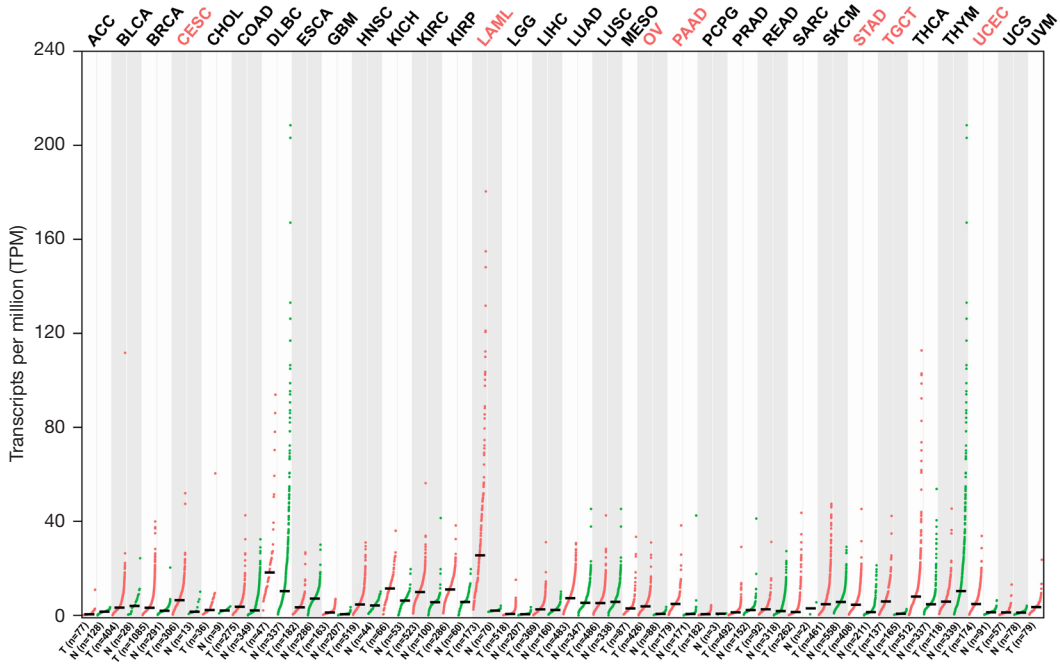

Figure 3 The expression of *ITGB7* in pan-cancer by a gene expression profiling interactive analysis.

carcinoma and endocervical adenocarcinoma, acute Myeloid leukemia, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, stomach adenocarcinoma, testicular germ cell tumors, and uterine corpus endometrial carcinoma (*Figure 3*). The results suggested that the expression of *ITGB7* might be relevant to the pathogenesis of these types of tumors.

Expression analysis of ITGB7 in BC

Compared to the normal samples, *ITGB7* was significantly upregulated in BC patients (*Figure 4A*). The results indicated that there was a close association between *ITGB7* and BC etiology. Additionally, compared to the normal samples, the expressions of ITGB7 in stages 1, 2, and 3 in the BC samples all differed significantly (*Figure 4B*).

Relationships between ITGB7 and the clinical features

No correlation was found between *ITGB7* expression and OS or RFS (P=0.073 and 0.64, respectively) (*Figures 5A,5B*). However, in terms of the relationship between *ITGB7* expression and different clinical features, the expression of *ITGB7* was associated with the menstrual status of the BC patients (P=0.012) (*Figure 5C*). Thus, *ITGB7* could function on the prognosis of BC patients with different menstrual statuses.

Discussion

BC has inter- and intra-tumoral heterogeneity, inconspicuous features in the early stages, and high mortality in later stages (1). As a closed-circle, nuclear, and non-plasmid DNA, eccNDA is ubiquitous in yeast, healthy humans, tumor samples, and cancer cells (9,10,20,21). There is increasing evidence that eccDNA might participate in the occurrence and progression of cancer; however, there are limited data on the role of eccDNA in the prognosis of BC patients (12,16). To the best of our knowledge, this was the first study to systematically examine the expression of eccDNA in BC and its association with the characteristics and prognosis of BC patients.

EccDNA plays an important role in tumor pathogenesis. It has a long half-life and stable biological structure that can carry a lot of genetic information (13). There is emerging evidence that eccDNA might propagate between cells through extracellular vesicles, thus forming more complex biological networks and promoting the development of tumor heterogeneity (13). Additionally, eecDNA might promote cancer evolution through the amplification of

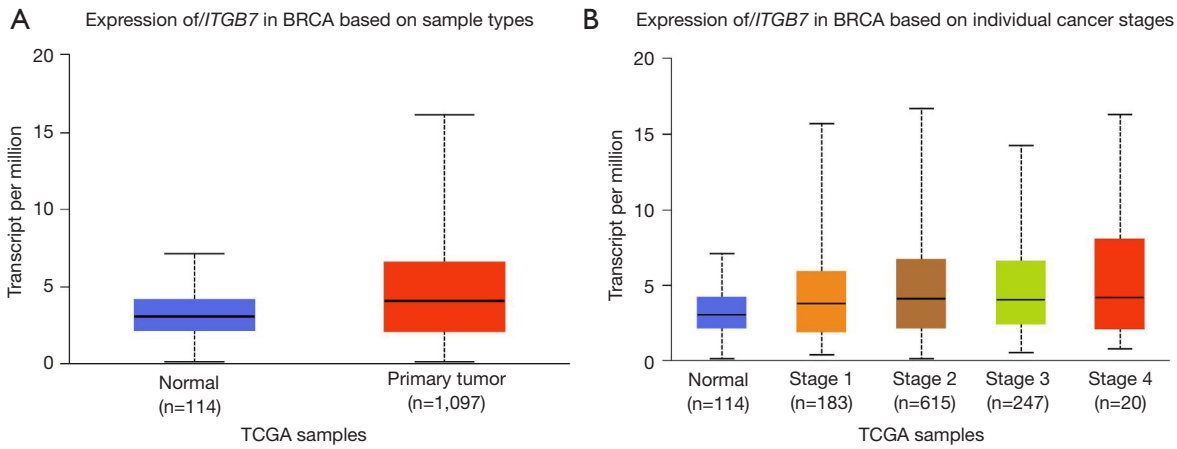

Figure 4 The expression of *ITGB7* in BC based on data from the University of ALabama at Birmingham CANcer data analysis Portal. (A) Groups based on sample types; (B) Groups based on cancer stages. BC/BRCA, Breast cancer; TCGA, The Cancer Genome Atlas.

oncogenes. For example, eccDNA was found to carry the epidermal growth factor receptor gene, which is an amplified oncogene in human cancer tissues (12,22). Surprisingly, the copy number of the epidermal growth factor receptor in eccDNA amplification was even higher than that in the chromosome amplicon (11,12). In addition, the eccDNAs mainly showed the extrachromosomal amplification of the drug-resistant genes, which may contribute to drug resistance in tumor cells (15).

In our study, many genes were found in the eccDNA genes, among which, *ITGB7* was the only ITGB family gene. ITGB is a subclass of integrin, which promotes the adhesion, proliferation, migration, and invasion of tumor cells, and regulates the permeability of endothelial cells (20,22). There is accumulating evidence that *ITGB7* plays an important role in the multiple cellular processes of various cancers, including colorectal cancer, pancreatic cancer, and cervical cancer (23-26). It is reasonable to speculate that *ITGB7* expression may be related to the evolution and prognosis of BC patients. However, the role of *ITGB7* on BC remains largely unknown. Thus, our study sought to further examine the role of *ITGB7* in all eccDNA genes.

We found that *ITGB7* was enriched in focal adhesion and human papillomavirus infection. Consistent with our results, two previous studies have shown that *ITGB7* regulates focal adhesion kinase signaling, thus accelerating pancreatic cancer and cervical cancer (24,25). Focal adhesion kinase, a cytoplasmic non-receptor tyrosine kinase, has been shown to be overexpressed in several cancer cells and to regulate cancer cell adhesion, motility, proliferation, and survival (27,28). Chai *et al.* also reported that human papillomavirus 16 regulated the *ITGB7*-CCAAT/enhancer binding protein-beta in cervical cancer (24). In addition, our study was the first to show that *ITGB7* was enriched in the ECM-receptor interaction and PI3K-Akt signaling pathway. The functions of these 2 signaling pathways in BC require further exploration.

Knowing evidence demonstrates that *ITGB7* may serve as novel biomarkers to shed new insights for early detection, monitoring of responses to drug treatment, and prognosis of cancer survival (15). Here, we investigated the relationship between *ITGB7* and patient prognosis in BC. Unexpectedly, *ITGB7* was not significantly associated with OS and RFS but was associated with the menstrual status of the BC patients. Recent research has shown that *ITGA7* overexpression appears to be associated with improved OS in patients with high-grade serous ovarian cancer, but the results were not statistically significant (15). *ITGB1* and *IGTB8* overexpression are associated with decreased RFS and OS. Zhu *et al.* showed that linc-*ITGB1* was significantly related to OS and disease-free survival in BC patients (29). In addition, other *ITGB* members have been shown to promote the skeletal metastasis of BC through gene expression modulation, enhance the invasion of cancer cells, and trigger glycolysis in cancer-associated fibroblasts, which may reduce OS and RFS in cancer (29-33). Based on previous reports, *ITGBs* might contribute to the poor prognosis of BC patients. Thus, further large-sample investigations need to be conducted to determine the effects of *ITGB7* on the prognosis of BC patients and to verify our findings.

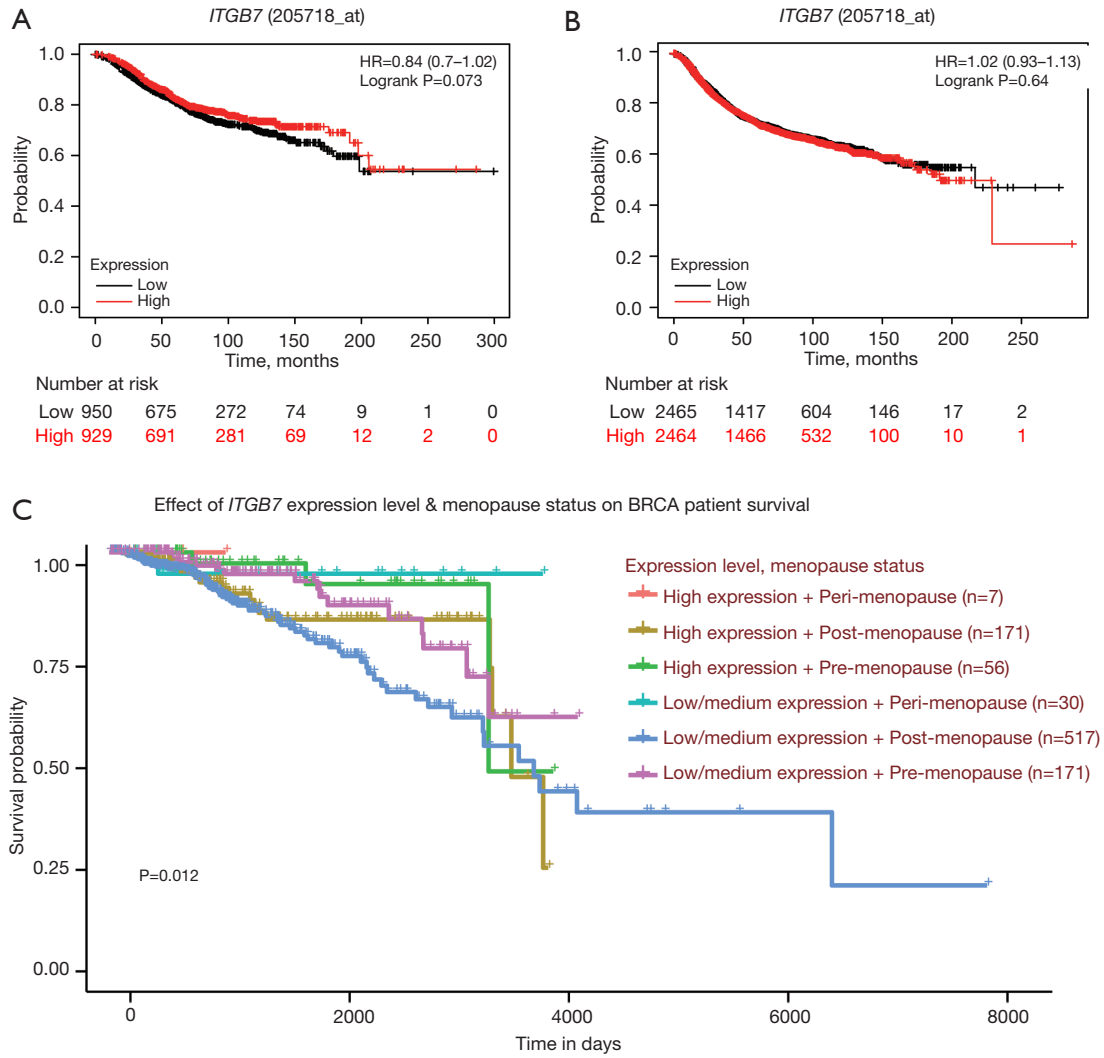

Figure 5 Kaplan-Meier curves showing the correlations between *ITGB7* expression and prognosis in BC patients. (A) Overall survival; (B) recurrence-free survival; (C) menopause status. BC/BRCA, breast cancer; HR, hazard ratio.

Conclusions

In the current study, we confirmed the significance of *ITGB7* in BC; however, it had several limitations that should be noted in interpreting the results. First, the relationships between *ITGB7* and some other important clinical characteristics, such as age and the tumor-node-metastasis staging of BC, were not analyzed in our study. Second, large differences in the number of normal samples and tumor samples, and tumor samples with various menstrual statuses and *ITGB7* expression levels may have created a bias in our results. Finally, our study did not demonstrate the potential mechanism by which *ITGB7* is involved in the development of BC, which requires further investigation.

In conclusion, *ITGB7* might serve as a prognostic marker for BC patients, and could have important implications for the individualized clinical treatment of BC patients. Further investigations should focus on eccDNAs as potential biomarkers and therapeutic targets for patients with BC.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5716/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5716/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5716/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee at The Second Affiliated Hospital of Air Force Medical University (No. K202010-04) and informed consent was taken from all the patients.

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