Original Article

Prognostic value of APOBEC3A in patients with cervical squamous cell carcinoma in a major urban center in China: a retrospective study

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Background: APOBEC3A (A3A) has been implicated to have vital prognostic value in several common cancers. This study aimed to investigate the prognostic value of A3A expression in cervical squamous cell carcinoma (CESC).

Methods: This retrospective study enrolled 59 patients with CESC or cervical squamous intraepithelial neoplasia from January 2014 to January 2017 in Changhai Hospital, Naval Medical University. Then, A3A histoscores (H-scores) using immunohistochemistry (IHC) were analyzed in formalin-fixed paraffin-embedded archival tissue blocks. Moreover, overall survival was analyzed by the Kaplan-Meier method.

Results: The H-score of A3A protein expression was relatively higher in CESC than in squamous intraepithelial neoplasia, and the relative expression level of normal cervical tissues was lower than that of cervical squamous intraepithelial neoplasia (P<0.001). Moreover, the H-score of poorly differentiated cases was 6, which was higher than that of moderately differentiated cases (H-score =3), while the H-score of well-differentiated cases was 2, which was lower than that of moderately differentiated cases. Moreover, patients in the A3A low expression group had higher overall survival rates by prognostic analysis (P=0.027).

Conclusions: A3A protein expression was increased during CESC progression. Moreover, A3A expression was tightly related to poor prognosis in CESC. Thus, these results showed that A3A overexpression may provide a marker for poor prognosis in CESC.

Keywords: Cervical squamous cell carcinoma (CESC); prognostic analysis; APOBEC3A (A3A); immunohistochemistry (IHC)

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Introduction

Death rates for female cervical cancers are considerably higher in transitioning versus transitioned countries (12.4 *vs.* 5.2 per 100,000) (1). Cervical squamous cell carcinoma (CESC) is the main pathological type of cervical cancer, which typically undergoes the progression from normal cervical lesions to cervical intraepithelial neoplasia (CIN) and then to the CESC. Fortunately, CESC, the most prominent pathological subtype of cervical cancer, has a decreasing incidence rate due to worldwide vaccination (2,3). However,

on the basis of the host of patients who have suffered from cervical lesions, it remains crucial to help patients prevent further deterioration of CESC. Therefore, it is of vital importance to clarify the underlying pathogenesis and provide molecular targeted therapy for CESC.

Human apolipoprotein-B mRNA-editing catalytic polypeptide-like 3 (APOBEC3) is a member of the enzyme family that converts cytosine of DNA and RNA into uracil (4-6). APOBEC3A (A3A) was initially considered to be a virus limiting factor capable of inhibiting the replication of endogenous retroviruses and reverse transcriptase (7,8). In ovarian cancer, A3A is recognized as a prognostic signature that correlates with genomic instability (9). A3A expression contributes to the poor prognosis and short survival of individuals with diffuse large B cell lymphoma (10). However, A3A overexpression attenuates biliary tract cancer progression by causing apoptosis (11). Thus, the role of A3A in cancers is complex and inconsistent (4,12-14).

After culture in differentiating condition, induction of A3A protein expression was found in W12 cells, a cervical dysplastic cell line (15). This indicated that A3A might affect the progression of cervical cancer lesions. The DNA deaminase activity of A3A also positively influences cervical cancer development and evolution, which has been demonstrated by a retrospective study (16). However, another study has found a relative deficit of APOBEC-related mutation signatures accompanying the transcriptional downregulation of A3A in recurrent/metastatic cervical tumors (17). Thus, the specific effect of A3A on the progression and deterioration of cervical lesions remains unclear.

A recent study showed that A3A deletion diminished A3-associated mutational signatures, with APOBEC3B (A3B) knock-out increasing A3A protein levels, activity, and A3A-mediated mutagenesis in bladder cancer and lymphoma cell lines (18). Therefore, in cervical cancer, we wondered if A3B affected the role of A3A. To explore this question, we conducted a retrospective and observational study to analyze the relationship between A3A expression and the occurrence of cervical cancer, with abnormalities in A3B expression. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-383/rc).

Highlight box

Key findings

- APOBEC3A (A3A) expression was tightly related to poor prognosis in cervical squamous cell carcinoma (CESC).

What is known and what is new?

- A3A is over-expressed in the non-Asian patients with CESC.
- A3A is over-expressed in the Chinese patients with CESC. The A3A expression fluctuate during the development of CESC.

What is the implication, and what should change now?

- These analyses reveal that A3A may be the new potential therapeutic target for cervical cancers. Due to the resource time limitation, this is a single-center retrospective study. Future prospective cohorts and multi-center studies will provide better evidence.

Methods

Study design and tissue procurement

The inclusion criteria were as follows: (I) patients who underwent radical hysterectomy or the loop electrosurgical excision procedure (LEEP) at the Department of Gynecology and Obstetrics of Changhai Hospital between January 2014 and January 2017; (II) patients with CESC or cervical squamous intraepithelial neoplasia aged less than 60 years old; and (III) patients who underwent radical hysterectomy whose cervical pathological reports showed normal cervical tissue. The exclusion criteria were as follows: (I) patients with CESC and CIN who were older than 60 years; (II) patients without radical hysterectomy or LEEP treatment; (III) patients' whose medical records were lost or incomplete; and (IV) those whose blocks of cervical tissue were broken or lost.

This retrospective study enrolled 59 patients with CESC or CIN from the Department of Gynecology and Obstetrics at Changhai Hospital, the Naval Medical University between January 2014 and January 2017. Twenty-five patients with normal cervical tissue were also involved. In total, 40 patients with cervical cancer underwent radical hysterectomy, while 19 patients with CIN received radical hysterectomy or cervical conization, and 25 patients with normal cervical tissues were chosen from patients who underwent radical hysterectomy for symptomatic uterine fibroids or adenomyosis. The 40 patients comprised 34 with CESC, 4 with cervical adenocarcinomas, 1 with high-grade neuroendocrine and 1

with cervical condyloma acuminatum specimens.

Collection of patient clinical information

Medical records of the 84 patients were collected regularly between 2019 and 2022. The clinical information contained personal identifiable information and clinicopathological data such as age, year of surgery, card number, pathology number, phone number, histological diagnosis, histological grade, tumor size, International Federation of Gynecology and Obstetrics (FIGO) stage, and lymph node metastasis.

Immunohistochemistry (IHC), quantification, and histoscores (H-scores)

In total, 84 blocks of cervical tissues from the 84 patients were obtained from the Tissue Bank of Changhai Hospital, Naval Medical University. All sections were counterstained with hematoxylin and photographed using a slide scanner (Servicebio, Woburn, MA, USA). Rabbit polyclonal anti-PHO1 (A3A) antibody (ab262853, 1:1,000 dilution; Abcam, Cambridge, UK) and rabbit polyclonal anti-A3B antibody (ab191695, 1:1,000 dilution; Abcam) were used (supplementary IHC data of 84 samples; available at https://cdn.amegroups.cn/static/public/tcr-23-383-1.pdf). The linear formula for H-score analysis is represented as follows: H-score =1 × (%weak-positive cells) + 2 × (%moderate-positive cells) + 3 × (%strong-positive cells), as previously described (12,13). If the %weak-positive cells were <25%, we considered it as 0. If the %weak-positive cells were between 25% and 49%, we considered it as 1. If the %weak-positive cells were between 50% and 75%, we considered it as 2. If the %weak-positive cells were greater than or equal to 76%, we considered it as 3 (Table S1). The A3A and A3B H-scores were evaluated by Professor Yongwei Yu from the Department of Pathology, Changhai Hospital and Professor Hongwei Zhang from the Department of Epidemiology, Naval Medical University and an attending physician in the Department of Obstetrics and Gynecology, Changhai Hospital.

Follow-up

For the first year after surgery, follow-up was performed every 3 months, then every 4 months for the second year, and every 6 months for years 3 through 5. After 5 years, follow-up was performed every year. During the 3 years of observation, we conducted telephone interviews three times for details of the patient's current status 5 years after surgery. Overall survival (OS) started on the date the sample was collected (surgical resection time).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Board of Naval Medical University (No. NMU-2020-13), and individual consent for this retrospective analysis was waived.

Statistical analysis

Chi-squared tests were used for categorical variables, while *t*-tests were used to examine differences between the numerical variables. P<0.05 was considered statistically significant. Moreover, the Kaplan-Meier method was used to analyze OS. We considered survival as the period elapsed from the time of first surgery to the last communication with the patient. Death was defined as an adverse event in the survival analysis. The object of the survival analysis was to identify the influence of A3A and A3B protein on the 5-year survival of cervical cancer patients. Five-year survival was analyzed with a 95% confidence interval. The software used for the statistical investigation was IBM SPSS 23.0 (Armonk, NY, USA). Kaplan-Meier analysis was performed using R v4.2.0. (www.r-project.org)

Results

Baseline information

In total, 84 specimens were tested via A3A IHC, including 40 CESC cases, 19 CIN cases, and 25 cases with normal cervical tissues. The operating times were between January 2014 and January 2017, while the majority of normal cervical tissues were taken around 2019. Analysis of baseline data was generated from 40 patients with CESC. The 40 CESC specimens were divided into the A3A high expression group (H-score >2, n=22) and A3A low expression group (H-score ≤2, n=18) via the relative H-scores of A3A protein expression (*Table 1*).

The median age of the cohort was 47 years old, with no statistically significant differences in the age of the patients in the A3A-high and -low expression groups (P=0.849) (*Table 1*). By statistical analysis, there was significant difference in the histological types between the A3A-high

Table 1 Baseline characteristics of patients with CESC (n=40)

Characteristics	L-A3A (n=18)	H-A3A (n=22)	P value
Age (years)			0.849
Median	47	47	
Range	32–60	38–59	
Histological grade, n (%)			0.003*
Well differentiated	4 (22.2)	0 (0.0)	
Moderately differentiated	13 (72.2)	10 (45.5)	
Poorly differentiated	1 (5.6)	8 (36.4)	
Unknown	0 (0.0)	4 (18.2)	
Tumor size (cm)			0.117
Median	2.0	2.5	
Range	1–4	2–6	
FIGO stage, n (%)			<0.001*
I	17 (94.4)	8 (36.4)	
II	1 (5.6)	7 (31.8)	
III	0 (0.0)	7 (31.8)	
Lymph node metastasis, n (%)			0.042*
0	18 (100.0)	14 (63.6)	
1	0 (0.0)	5 (22.7)	
2	0 (0.0)	1 (4.5)	
Unknown	0 (0.0)	2 (9.1)	

*, P value <0.05. CESC, cervical squamous cell carcinoma; L-A3A, low level of human APOBEC3A (< median expression level); H-A3A, high level of human APOBEC3A (≥ median expression level); APOBEC3, apolipoprotein-B mRNA-editing catalytic polypeptide-like 3; FIGO, Federation of Gynecology and Obstetrics.

and -low expression groups (P=0.003) (*Table 1*). Differences in the H-scores of tumor size between the A3A-high and -low expression groups were also not significantly different (P=0.117) (*Table 1*).

Remarkably, well-differentiated histological grade carcinoma specimens were concentrated in the A3A-low expression group, while the majority of poorly differentiated histological grade carcinoma specimens were concentrated in the A3A-high expression group. Among the 22 patients in the A3A-high expression group, there were 10 (45.5%) diagnosed with moderately differentiated histological grade carcinoma. In contrast, 13 (72.2%) of the 18 specimens in the A3A-low expression group were diagnosed as moderately differentiated carcinoma, which represented a significantly higher A3A-positivity rate in patients diagnosed with moderately differentiated carcinoma (P=0.003) (*Table 1*). As tumor stage progressed, A3A protein levels in patients with CESC increased (P<0.001) (*Table 1*). Altogether, there were 17 of 25 FIGO stage I carcinoma specimens in the A3A-low expression group, which covered 94.4% the A3A low expression group. The H-scores of seven samples of the eight FIGO stage II and seven samples of the seven FIGO stage III patients were in the A3A-low expression group, which covered 31.8% of the A3A-high expression group. Finally, no lymph node metastasis occurred in any of the A3A-low expression patients. There were 5 (22.7%) patients in the A3A-high expression group with one lymph node metastasis, compared with only one patient (4.5%) with two lymph node metastases. A statistical comparison of H-scores among patients with lymph node metastases between the A3A-low and -high expression groups was also conducted (P=0.042) (*Table 1*).

Immunohistochemical detection of endogenous A3A protein during disease progression

When we tested the A3A H-scores of specimens via A3A IHC, the results indicated that high expression of A3A protein occurred in cancer cells from clinical samples. H-scores also reached their maximum value of 6. Interestingly, A3A protein expression increased during disease progression. A3A protein expression was relatively higher in CESC than in squamous intraepithelial neoplasia (*Figure 1*). In CESC, there were also significant differences in A3A protein expression between histologic subtypes (*Table 1*). H-scores of poorly differentiated CESC were 6, which was higher than that of moderately differentiated cases (H-score =3). H-scores of well-differentiated CESC were 2, which was lower than that of moderately differentiated CESC (*Figure 1*). Thus, A3A was associated with the development of CIN into squamous cell carcinoma.

H-scores were tested by two professors and an attending physician, and A3A had relatively higher expression in CESC specimens compared with CIN lesions and normal tissues (P<0.001) (*Figure 2*). However, no significant differences in relative A3A expression were found between the CIN III and CIN I–II groups (P=0.197). It was also estimated that the relative expression of A3B was higher in CESC than in CIN lesions and normal tissues (P<0.001); however, there was no significant difference between the CIN III and CIN I–II groups (P=0.196) (*Figure 2*). In

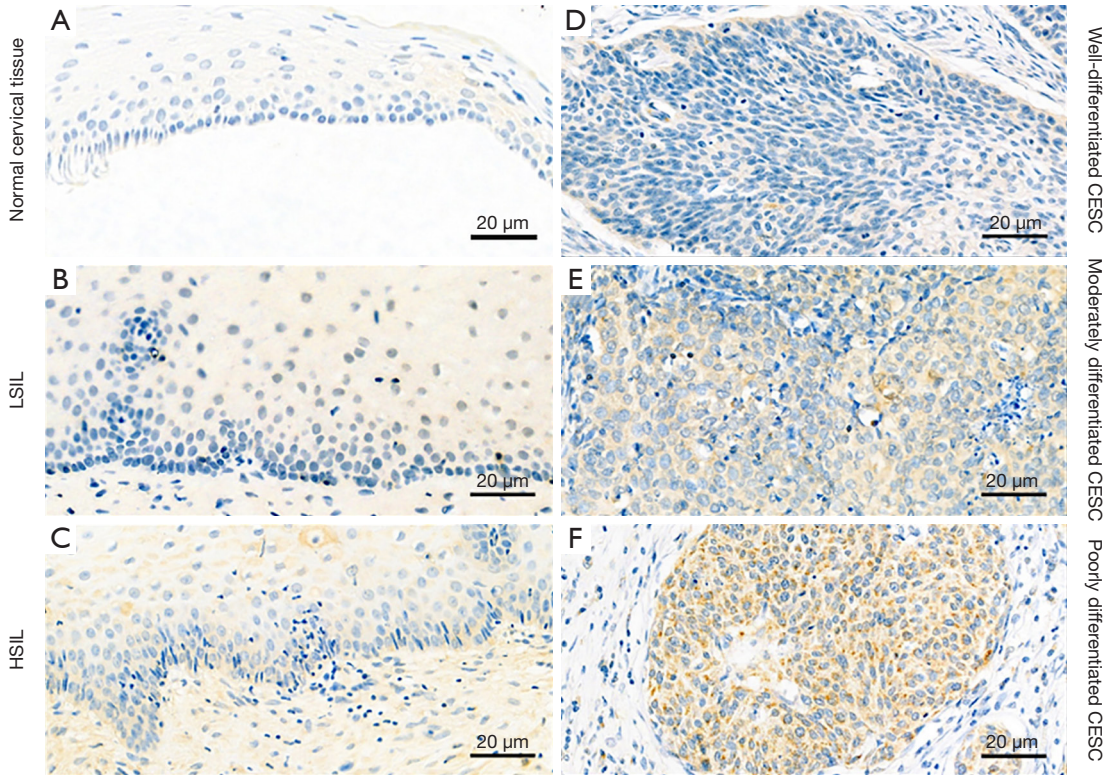

Figure 1 IHC detection of endogenous A3A protein expression in normal cervical tissue, intraepithelial neoplasia, and squamous cell carcinoma of the cervix. (A) A3A H-score in normal cervical tissue: H-score =0. (B) A3A H-score in an LSIL: H-score =2. (C) A3A H-score in HSIL: H-score =3. (D) A3A H-score in well-differentiated CESC. H-score =2. (E) A3A H-score in moderately differentiated CESC: H-score =3. (F) A3A H-score in poorly differentiated CESC: H-score =6. Scale bars are measured 20 μm. IHC, immunohistochemistry; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CESC, cervical squamous cell carcinoma; A3A, human APOBEC3A; APOBEC3, apolipoprotein-B mRNA-editing catalytic polypeptide-like 3; H-score, histoscore.

summary, there were similar changes in A3A and A3B expression during disease progression. There was no statistical difference in A3A and A3B expression when cervical lesions progressed within the scope of precancerous lesions. A3A and A3B may play important roles in the occurrence of CESC because they both show significantly high expression in CESC.

High A3A expression as an indicator for worse prognosis in CESC

In total, 87% of the 84 enrolled patients reached their follow-up visits, while 11 patients died during follow-up. For CESC and cervical squamous intraepithelial neoplasia patients, the median age was 49 years (range, 31–59 years). At the time of data cutoff, the median OS was 94 months for CESC patients. Among the 22 patients in the A3A-high expression group, the 36-month OS rate was 95.5% and the 60-month OS rate was 81.8%. For the 18 patients in the A3A-low expression group, the 3-year survival rate was 100% and the 5-year survival rate was 88.9%. Patients in the A3A-low expression group has a higher OS rate (*Figure 3*), which indicated A3A to be a predictor of worse prognosis and survival in CESC patients. No difference in OS was observed between the A3B-high and -low expression groups.

Discussion

With the development of gene sequencing technology, various accumulating somatic mutations have been discovered during tumorigenesis, which can now being interrogated for their role in disease progression (19). The propensity of increased tumor cell mutations by

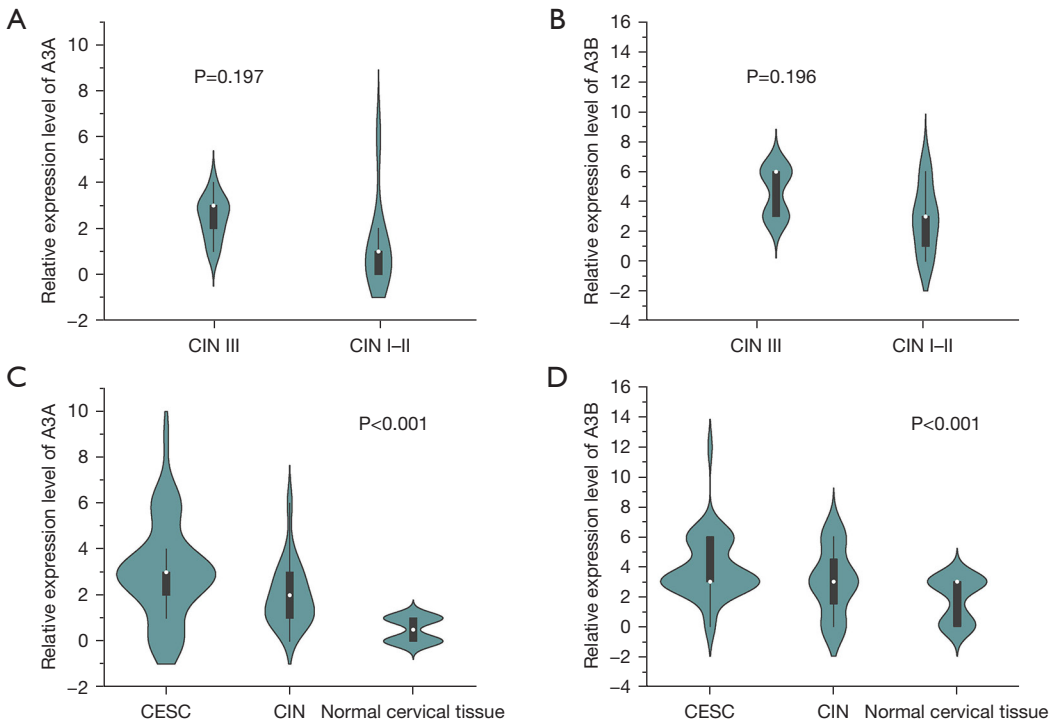

Figure 2 A3A expression H-score in different histological types of cervical cancer. (A) The H-score of A3A protein expression in moderately differentiated CESC: H-score =3. (B) The H-score of A3B protein expression moderately differentiated adenocarcinoma of the uterine cervix. (C) The H-score of A3A protein expression in high-grade neuroendocrine carcinoma of the uterine cervix. (D) The H-score of A3B protein expression in warty (condylomatous) carcinoma of the uterine cervix. A3A, human APOBEC3A; A3B, human APOBEC3B; APOBEC3, apolipoprotein-B mRNA-editing catalytic polypeptide-like 3; CIN, cervical intraepithelial neoplasia; CESC, cervical squamous cell carcinoma; H-score, histoscore.

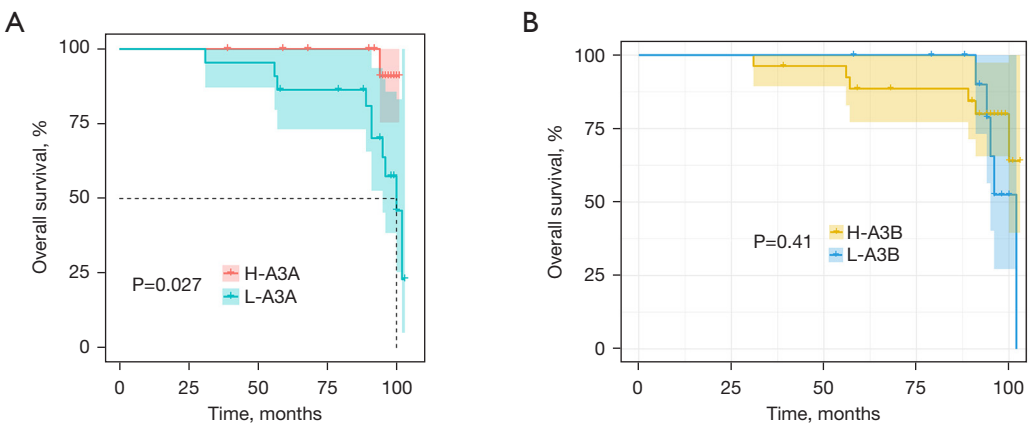

Figure 3 Overall survival. Kaplan-Meier estimates of survival outcomes in patients with cervical carcinoma (n=40). The minimum survival time was 31 months, and the maximum survival time was 103 months. P value <0.05. H-A3A, high level of human APOBEC3A (≥ median expression level); L-A3A, low level of human APOBEC3A (< median expression level); H-A3B, high level of human APOBEC3B (≥ median expression level); L-A3B, low level of human APOBEC3B (< median expression level); APOBEC3, apolipoprotein-B mRNA-editing catalytic polypeptide-like 3.

aberrant DNA editing has been attributed to the activity of APOBEC-related DNA-editing proteins (14,20), which has particular roles in gynecological malignant tumors (18,21,22). Recently, cervical tissue with weak or negative A3A protein expression has been reported to be prominently involved in increased susceptibility to cervical cancer (22). Some researchers believe DNA damage induced by A3A to be the major driver of iterative somatic mutations across many cancers, including cervical cancer, which represents the significance of A3A in cervical cancer mutagenesis (22). Studies have confirmed that the A3A mutational characteristics of murine tumor models are similar to the APOBEC mutational characteristics of human cervical cancer, providing additional evidence that this DNA deaminase plays an active role in the development and evolution of human tumors (4,18). However, some findings have suggested that A3A acts as a restriction factor against human papillomavirus (HPV) infection (23), and this supposes a downregulation of A3A might be associated with unfavorable clinical outcomes in CESC (17,18). Thus, it remains unclear whether A3A protects from CESC or may be a potential molecular target for anti-cancer therapy.

This study enrolled patients at Changhai Hospital because of cervical lesions from early 2014 to 2017. Patient age was limited to ≤60 years, to remove any impact of underlying disease. We were surprised to discover that a large number of patients fitted the criteria. Moreover, we gathered detailed medical records of the initial operation and classified them according to clinical characteristic. Subsequently, we used 84 blocks from the Pathology Department of Changhai Hospital, including 25 normal cervical tissues as controls. Baseline characteristics of patients with CESC are listed in *Table 1*. A3A protein expression was significantly different across the following parameters: histological grade (P=0.003), FIGO stage (P=0.001), and lymph node metastasis (P=0.042). Remarkably, the H-scores of A3A increased with FIGO stage, which ultimately showed that A3A was associated with CESC progression.

To uncover the role of A3A in CESC, follow-up was conducted regularly during 3 years between June 2019 and June 2022. The majority of patients actively engaged in telephone follow-up surveys. On the basis of information from patients in the Gynecology Department of Changhai Hospital, A3A protein level can be implicated in the prognosis of CESC. The tissue samples from tumor patients in the UK and the United States showed that a role for A3A in human cancer seems more likely than for other members of the family on the basis of similarities in the sequence context of cytosine mutations caused by APOBEC enzymes in experimental systems (24). The prevalence of A3A deletion polymorphism has been reported to be 40.1% in Indonesia, 6% in Europe, 37% in East Asians, 34.5% in India, 57.1% in America, and 93% in Oceania (25).

Moreover, A3B, which has a mutational signature similar to A3A, has also been implicated in cancer-associated mutations (11,13,19). In our study, A3B protein expression had similar changes to A3A protein expression during the occurrence of CESC. However, A3B protein do not have prognostic influence on the OS of CESC patients, which may be inconsistent with the function of A3A protein. Additionally, another recent study showed that A3B deficiency promoted A3A protein levels, activity, and A3A-mediated mutagenesis in some cell lines (12). Therefore, the interaction between A3A and A3B proteins in CESC is particularly important and should be further researched (12).

In summary, A3A had positive and crucial associations with the occurrence and development of cervical cancer. Although A3A showed low protein expression in CESC, cervical squamous intraepithelial neoplasia, and normal cervical tissues, A3A expression was increased with cervical cancer progression. A3A expression was also tightly related to poor prognosis in CESC. Overall, our results showed that A3A overexpression could be a marker for poor prognosis in CESC. Finally, A3B protein expression was increased with CESC progression, suggesting it may affect A3A protein levels in the disease state.

Conclusions

A3A protein expression was higher in CESC than in normal cervical tissues. High A3A protein expression was associated with poorly differentiated cervical cancer, advanced stage CESC (FIGO stage II–III), and was also significantly related to worse OS. In conclusion, A3A appears to play crucial roles in the occurrence and development of cervical cancer, especially CESC.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-383/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-383/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-383/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 Institutional Ethics Board of Naval Medical University (No. NMU-2020-13), and individual consent for this retrospective analysis was waived.

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