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Keratin-15 high expression links with lymph node metastasis and poor survival prognosis in epithelial ovarian cancer patients

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Abstract

Background Keratin-15 (KRT15) involves in the progression and owns prognostic values in several solid cancers, whose clinical role in epithelial ovarian cancer (EOC) is rarely reported. This study aimed to identify the association of KRT15 expression with tumor features and survival of surgical EOC patients.

Methods Formalin-fixed paraffin-embedded tumor tissues of 140 EOC patients who underwent tumor resection were retrieved for KRT15 determination using immunohistochemistry (IHC) assay.

Results The median (interquartile range) KRT15 IHC score was 0.0 (0.0–1.0), ranging from 0.0 to 12.0. Among all, 36.4% of patients had positive KRT15 expression (IHC score > 0) and 15.0% of patients had high KRT15 expression (IHC score > 3). KRT15 was positively related to lymph node metastasis incidence ($P = 0.027$), and showed a tendency to correlate to FIGO stage but without statistical significance ($P = 0.052$), while it was not correlated with age, other tumor features, and tumor markers. Positive KRT15 expression was linked with poor disease-free survival (DFS) ($P = 0.009$) and overall survival (OS) ($P = 0.032$). Notably, high KRT15 expression showed an even stronger relationship with worse DFS ($P = 0.001$) and OS ($P < 0.001$). After adjustment of multivariable Cox's regression, high KRT15 expression was independently correlated with unfavorable DFS (hazard ratio (HR): 2.241, $P = 0.007$).

Conclusion Even though KRT15 is insufficiently expressed in EOC tissues generally, its positive expression or high expression can predict the lymph node metastasis and poor survival prognosis in EOC patients who undergo tumor resection.

Keywords Epithelial ovarian cancer · Keratin-15 · Disease features · Disease-free survival · Overall survival

1 Introduction

Ovarian cancer is among the most prevalent and lethal gynecologic cancers [1]. Annually, there is an estimated of 57,090 and 24,494 newly diagnosed ovarian cancer patients in China and the United States, respectively [2]. Epithelial ovarian cancer (EOC), originating from the ovarian surface epithelium, accounts for nearly 90% of all ovarian cancer cases [3–5]. Currently, the primary treatment for EOC patients is tumor resection followed by adjuvant chemotherapy [6–9]. However, a proportion of EOC patients who undergo tumor resection experience recurrence and suffer from a poor survival [10,

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11]. Consequently, exploring markers with the ability for predicting recurrence and survival is meaningful to provide individualized therapy for EOC patients who undergo tumor resection [12, 13].

Keratin-15 (KRT15), a type I cytoskeletal protein, is mainly expressed in the keratinocytes in stratified epithelia and regulates proliferation, differentiation and regeneration of basal cells [14–17]. Intriguingly, KRT15 participates in tumorigenesis and tumor migration of various cancers, which also reflects dismal prognosis in cancer patients [18–21]. For instance, a study reveals that KRT15 may exert a tumor-initiating function in mouse intestinal cancer models [18]. Another research discloses that KRT15 facilitates migration of colorectal cancer via β-catenin/matrix metallopeptidase 7 signaling pathway [19]. Clinically, a study suggests that increased KRT15 links with poor survival in endometrial cancer patients [20]. Another clinical study indicates that elevated KRT15 expression estimates worse prognosis of colorectal cancer patients [21].

Considering the following aspects: (1) KRT15 is a cytoskeletal and microfibrillar protein (www.uniprot.org/uniprotkb/P19012/entry), its structure feature is related to tumor growth and invasion. (2) KRT15 has been reported to be an oncogene and prognostic marker in a number of cancers [18–21]. (3) KRT15 also shows potency to be a prognostic marker in gynecological cancers such as endometrial cancer and ovarian cancer [20, 22, 23]. Therefore, as another typical gynecological cancer, it's hypothesized that KRT15 also has a prognostic value in ovarian cancer. However, the clinical value of KRT15 in ovarian cancer patients is unknown.

Therefore, this study detected KRT15 expression in EOC patients who underwent tumor resection, aiming to identify its relation to tumor features and survival prognosis in these patients.

2 Materials and methods

2.1 Participants

This retrospective study screened 140 patients with EOC who underwent tumor resection between May 2018 and Sep 2022. Patients who met the following criteria were included: (a) confirmed as primary EOC; (b) aged ≥ 18 years; (c) underwent tumor resection; (d) accessible cancer tissue samples before treatment. Patients who met one of the following criteria were excluded: (a) no record of any follow-up visits; (b) had other primary malignant tumors; (c) pregnant or lactating women. The Ethics Committee of The First Affiliated Hospital of Yangtze University approved the study. The study was carried out following the guidelines of the Ethics Committee. All patients or direct relatives provided the informed consent.

2.2 Data collection and sample processing

The study collected clinical characteristics of patients from the hospital's electronic medical record system, then obtained formalin-fixed paraffin-embedded (FFPE) tumor tissues and cut into sections. The immunohistochemistry (IHC) was used for detecting the KRT15 expression. The KRT15 rabbit monoclonal antibody was purchased from Biotend company (Shanghai, China), the goat-anti-rabbit immunoglobulin G antibody was purchased from Fusheng Biotech company (Shanghai, China). The staining images were stained and observed under a light microscope.

2.3 Krt15 IHC score

The intensity of staining was scored as 0, 1, 2, 3 referring to no staining intensity, weak staining intensity, moderate staining intensity, and strong staining intensity, respectively; the density of staining was scored as 0, 1, 2, 3, 4 referring to 0% staining density, 1–25% staining density, 26–50% staining density, 51–75% staining density, and 76–100% staining density, respectively. Then, the final IHC score was calculated by multiplying the staining intensity score and density score, resulting in 0–12 points score [24]. KRT15 IHC score was scored by 2 evaluators who were completely unaware of the study, the mean of the scores was taken as the final score.

Patients in this study had a generally low KRT15 expression levels. The median value of the KRT15 IHC score was 0.0 and the interquartile range (IQR) was 0.0–1.0. In order to better analyze the prognosis of patients, we used two different cutoff values of 0 and 3 to group patients. KRT15 IHC score > 0 was determined as a positive KRT15 expression, while KRT15 IHC score = 0 was determined as a negative KRT15 expression. KRT15 IHC score > 3 was determined as a high KRT15 expression, while KRT15 IHC score ≤ 3 was determined as a low or no KRT15 expression.

2.4 Follow-up and evaluation

Follow-up data were collected from patients in this study. The routine assessment was conducted at the time of the end of 3-cycle adjuvant therapy, the end the total adjuvant therapy, then every 3 months to 2 years, then every 3–6 months to 5 years. The last follow-up date was May 2023. Then, the disease status was evaluated. The disease-free survival (DFS) and overall survival (OS) were calculated. The definition of DFS was the time from surgery to EOC recurrence or death, whichever occurred first. The definition of OS was the time from surgery to death from any cause. A month was calculated as 30 days in the survival analysis.

2.5 Statistics

The study used SPSS V.23.0 (IBM Corp., USA) for data analysis. Data presentation on patient clinical characteristics: age was presented as mean ± standard deviation (SD), KRT15 IHC score was presented as a median, IQR and range, and the categorized variables were presented as count (percentage). Comparative analyses were determined by the Mann–Whitney U or the Kruskal Wallis tests. Kaplan Meier curves were plotted to show the DFS or OS in patients with different KRT15 expression levels (low vs. high expression and negative vs. positive expression). Univariable and forward stepwise multivariable Cox proportional hazards regression model analyses were used for assessing parameters associated with DFS or OS, the included parameters were required to have at least 10 events in each level of categorizations to generate reliable results, otherwise excluded. All reported tests were two-tailed, and P value < 0.05 was considered statistically significant.

3 Results

3.1 Characteristics

A total of 140 EOC patients with a mean age of 62.1 ± 9.2 years were enrolled in this study (Table 1). A respective of 102 (72.9%), 16 (11.4%), 12 (8.6%), and 10 (7.1%) patients were identified as high-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and other types of carcinomas. Tumor size of 37 (26.4%) patients was > 10 cm. Besides, 81 (57.9%) patients were recognized as peritoneal cytology positivity, and 79 (56.4%) patients had lymph node metastasis. Additionally, 51 (36.4%) patients were at international federation of gynecology and obstetrics (FIGO) stage I-II, whereas 89 (63.6%) patients were at FIGO stage III-IV. Moreover, 122 (87.1%), 102 (72.9%), and 101 (72.1%) patients had abnormal cancer antigen 125 (CA125), cancer antigen 199 (CA199), and carcinoembryonic antigen (CEA), correspondingly. Lastly, 133 (95.0%) patients received adjuvant therapy.

3.2 Krt15 expression

The median (IQR) KRT15 IHC score was 0.0 (0.0–1.0), ranging from 0.0 to 12.0 (Fig. 1A). Among all, 36.4% of patients had positive KRT15 expression (Fig. 1B) and 15.0% of patients had a high KRT15 expression (Fig. 1C). The IHC images of negative, positive (but not high), and high KRT15 expression are showed in Fig. 1D. Besides, the characteristics between KRT15 negative group and KRT15 positive group, and between KRT15 low or no group and KRT15 high group are presented in Supplementary Table 1.

3.3 Correlation of krt15 expression with disease features

KRT15 expression was positively correlated with lymph node metastasis ($P = 0.027$), and exhibited a tendency to be positively correlated with FIGO stage ($P = 0.052$), but without statistical significance; while it was not related to age ($P = 0.625$), histological type ($P = 0.074$), tumor size ($P = 0.208$), peritoneal cytology ($P = 0.211$), abnormal CA125 ($P = 0.605$), abnormal CA199 ($P = 0.150$), abnormal CEA ($P = 0.656$), or adjuvant therapy ($P = 0.731$) (Fig. 2A–J).

Table 1 EOC patients' characteristics

Items	EOC patients (*N* = 140)
Age (years), mean ± SD	62.1 ± 9.2
Histological type, n (%)	
High-grade serous carcinoma	102 (72.9)
Endometrioid carcinoma	16 (11.4)
Clear cell carcinoma	12 (8.6)
Others	10 (7.1)
Tumor size > 10 cm, n (%)	37 (26.4)
Peritoneal cytology positivity, n (%)	81 (57.9)
Lymph node metastasis, n (%)	79 (56.4)
FIGO stage, n (%)	
I-II	51 (36.4)
III-IV	89 (63.6)
Abnormal CA125, n (%)	122 (87.1)
Abnormal CA199, n (%)	102 (72.9)
Abnormal CEA, n (%)	101 (72.1)
Adjuvant therapy, n (%)	133 (95.0)
Docetaxel + carboplatin	69 (49.3)
Paclitaxel + carboplatin	33 (23.6)
Liposomal doxorubicin + carboplatin	23 (16.4)
Paclitaxel + carboplatin + bevacizumab	8 (5.7)

EOC, epithelial ovarian cancer; SD, standard deviation; FIGO, international federation of gynecology and obstetrics; CA125, cancer antigen 125; CA199, cancer antigen 199; CEA, carcinoembryonic antigen

3.4 Prognostic value of krt15 expression

Positive KRT15 expression was associated with poor DFS ($P = 0.009$) (Fig. 3A). Notably, high KRT15 expression was related to even worse DFS ($P = 0.001$) (Fig. 3B). Meanwhile, positive KRT15 expression was linked with unfavorable OS ($P = 0.032$) (Fig. 3C). High KRT15 expression was also correlated with worse accumulating OS ($P < 0.001$) (Fig. 3D).

In addition, we screened out the high-grade serous carcinoma patients, then analyzed the correlation of KRT15 expression with prognosis in them. Positive KRT15 expression showed a tendency to be correlated with worse DFS, but did not reach the statistical significance ($P = 0.063$) (Supplementary Fig. 1A), while high KRT15 expression was significantly associated with unfavorable DFS ($P = 0.025$) (Supplementary Fig. 1B). Similarly, positive KRT15 expression showed a tendency to be correlated with worse OS, but did not reach the statistical significance ($P = 0.154$) (Supplementary Fig. 1C), while high KRT15 expression was significantly associated with unfavorable OS ($P = 0.015$) (Supplementary Fig. 1D).

3.5 Factors predicting DFS

Positive KRT15 expression (yes vs. no) (hazard ratio (HR): 1.885, $P = 0.010$), high KRT15 expression (yes vs. no) (HR: 2.519, $P = 0.001$), tumor size > 10 cm (yes vs. no) (HR: 2.043, $P = 0.005$), peritoneal cytology (positive vs. negative) (HR: 2.021, $P = 0.009$), lymph node metastasis (yes vs. no) (HR: 2.521, $P = 0.001$), and FIGO stage (III-IV vs. I-II) (HR: 2.316, $P = 0.004$) were linked with worse DFS (Fig. 4A). Further multivariable Cox's regression analysis revealed that high KRT15 expression (yes vs. no) (HR: 2.241, $P = 0.007$), tumor size > 10 cm (yes vs. no) (HR: 2.072, $P = 0.006$), peritoneal cytology (positive vs. negative) (HR: 1.752, $P = 0.042$), and lymph node metastasis (yes vs. no) (HR: 2.610, $P = 0.001$) were independently associated with worse DFS (Fig. 4B).

3.6 Factors predicting OS

Positive KRT15 expression (yes vs. no) (HR: 2.133, $P = 0.036$), high KRT15 expression (yes vs. no) (HR: 3.688, $P = 0.001$), tumor size > 10 cm (yes vs. no) (HR: 2.114, $P = 0.043$), were correlated with worse OS (Fig. 5).

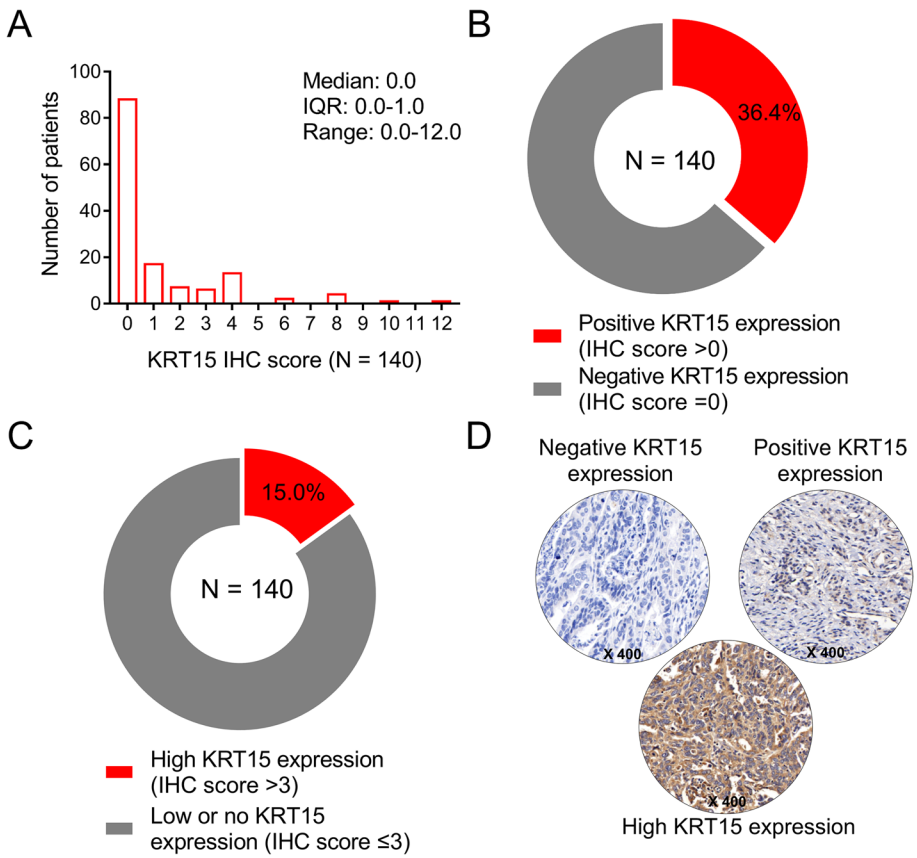


Fig. 1 KRT15 IHC score in EOC patients. The distribution of KRT15 expression in EOC patients (**A**). The proportion of EOC patients with positive KRT15 expression (**B**). The proportion of EOC patients with high KRT15 expression (**C**). The IHC examples of negative, positive, and high KRT15 expression tissues of EOC patients (**D**)

4 Discussion

Available evidence suggests that KRT15 exerts a function in the development of malignancy, meanwhile, several studies detect KRT15 expression in cancer patients, which may be meaningful to identify potential markers to predict prognosis of cancers [20, 21, 25, 26]. For instance, a study reveals that the median (IQR) KRT15 IHC score of tumor tissue is 4.0 (3.0–8.0) in endometrial cancer patients [20]. Another study observes that 57.1% colorectal cancer patients have an elevated KRT15 expression [21]. Nonetheless, limited studies quantify KRT15 in EOC patients. In this study, the median (IQR) KRT15 IHC score of EOC patients who underwent tumor resection was 0.0 (0.0–1.0). Only 36.4% of EOC patients had positive KRT15 expression, and 15.0% of EOC patients had a high KRT15 expression. The aforementioned findings indicated that the level of KRT15 expression was inconsistent among different types of cancer, which might be attributed the distinct mechanisms of KRT15 on regulating malignant phenotypes in different cancers. However, this speculation needed further studies to validate.

Previous studies report that increased KRT15 expression is associated with unfavorable tumor features of cancer patients [20, 21, 24, 27]. For example, a recent study observes that higher KRT15 is linked to lymph node metastasis in esophageal cancer patients [27]. Another study notices that KRT15 expression is positively related to lymph node metastasis and clinical stage of colorectal cancer patients [21]. Similarly, the current study identified that elevated KRT15 expression was correlated with lymph node metastasis in EOC patients who underwent tumor resection. The possible reasons might be: KRT15 overexpression enhanced invasive potential and migration potency of tumor cells, contributing to lymph node metastasis of patients [19, 24, 28]. Therefore, increased KRT15 expression was associated with lymph node metastasis of EOC patients who underwent tumor resection.

Apart from the correlation of KRT15 with unfavorable tumor features, several studies illustrate the prognostic value of KRT15 in cancer patients [20, 24, 29, 30]. For example, a study detects KRT15 protein expression in 135 surgical endometrial cancer patients, indicating that high KRT15 protein is independently correlated to shorter DFS and OS in endometrial cancer patients [20]. Another study suggests that KRT15 IHC score > 3 can predict worse DFS and OS in patients with renal cell carcinoma [24]. The current study revealed that positive KRT15 expression

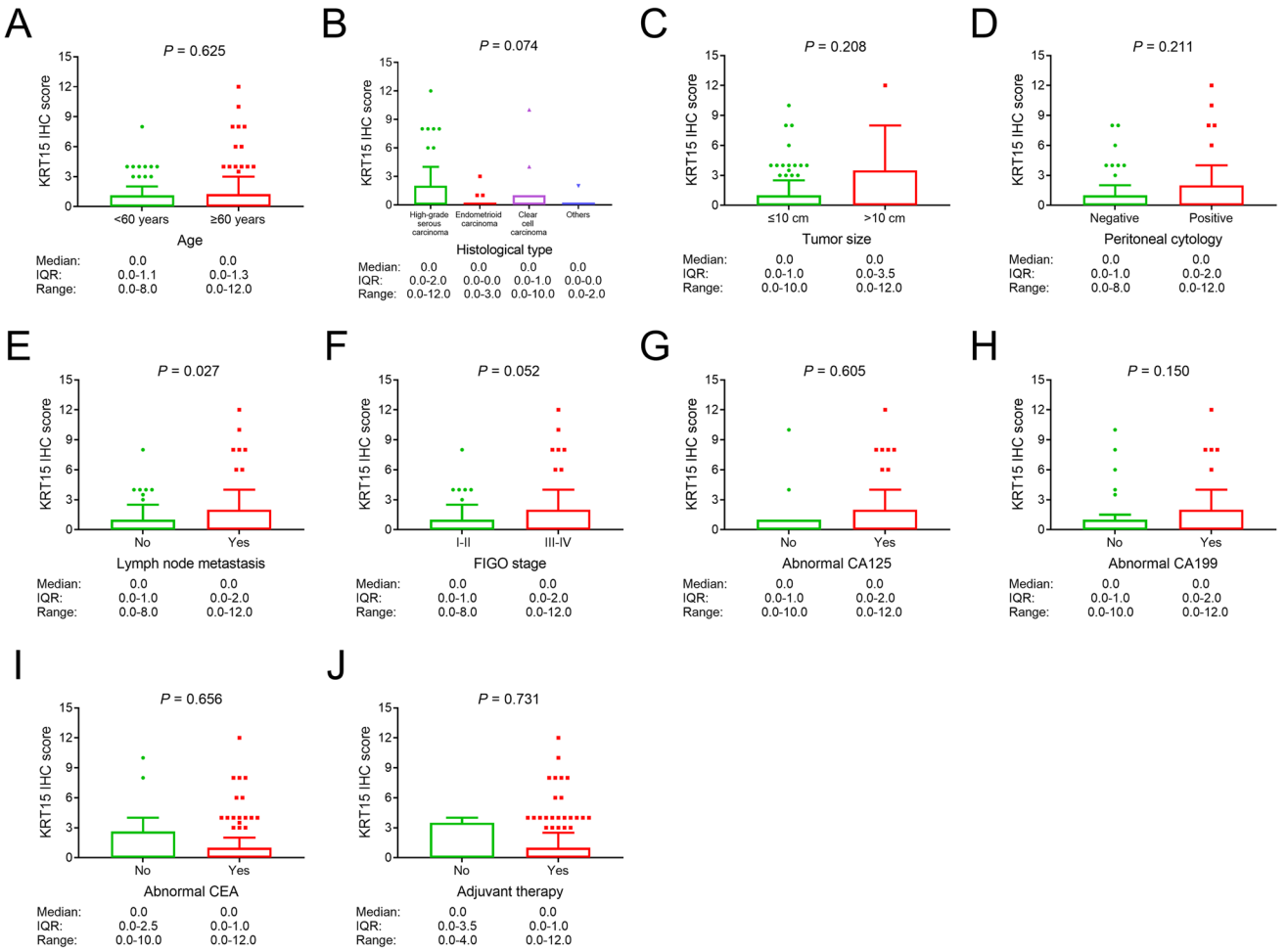


Fig. 2 KRT15 expression positively linked with lymph node metastasis in EOC patients. Correlation of KRT15 expression with age (**A**), histological type (**B**), tumor size (**C**), peritoneal cytology (**D**), lymph node metastasis (**E**), FIGO stage (**F**), abnormal CA125 (**G**), abnormal CA199 (**H**), abnormal CEA (**I**), and adjuvant therapy (**J**) in EOC patients

(IHC score > 0) was linked with worse DFS and OS of EOC patients who underwent tumor resection; furthermore, high KRT15 expression (IHC score > 3) exerted an even stronger prognostic value and was independently related to shorter DFS of EOC patients who underwent tumor resection. The results could be explained as follows: (1) KRT15 potentiated stem cell property to incur recurrence in cancer patients, leading to worse DFS of them [20]. (2) According to the findings of this study, KRT15 was associated unpleasing tumor features, such as lymph node metastasis, leading to worse survival of EOC patients. Hence, increased KRT15 expression possessed a capability for estimating worse survival of EOC patients who underwent tumor resection. Moreover, extreme high expression of KRT15 substantially facilitated tumor progression, leading to even worse survival of EOC patients. Therefore, high KRT15 expression had an intensified ability for predicting survival of EOC patients who underwent tumor resection. It should be pointed out that the explanation was speculations based on the previous studies, but not direct evidence; therefore, more deep investigations were needed. However, the results of Cox regression analyses were not corrected for multiplicity due to lack of evidence for the method choice; therefore, some findings should be further validated in a larger study.

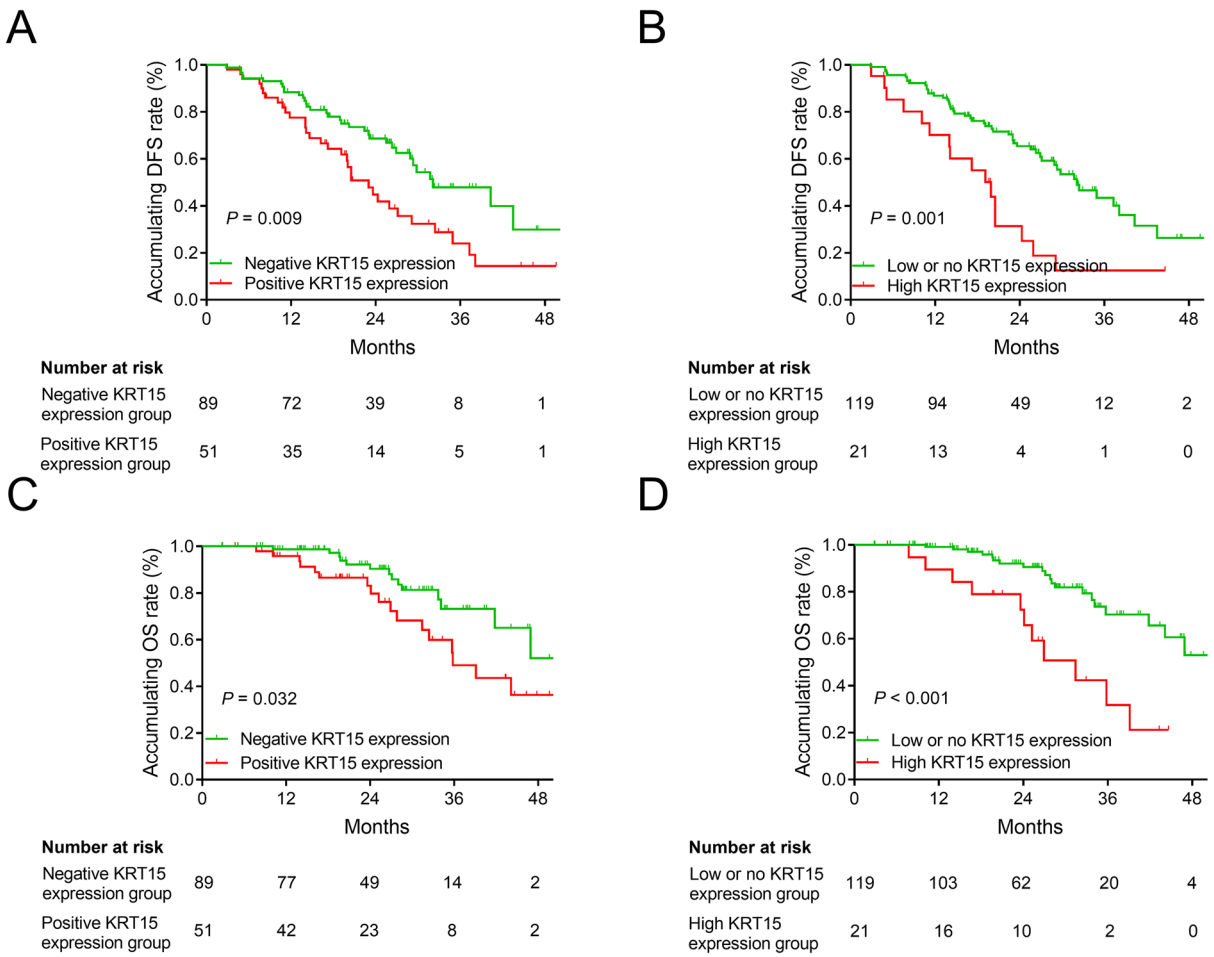


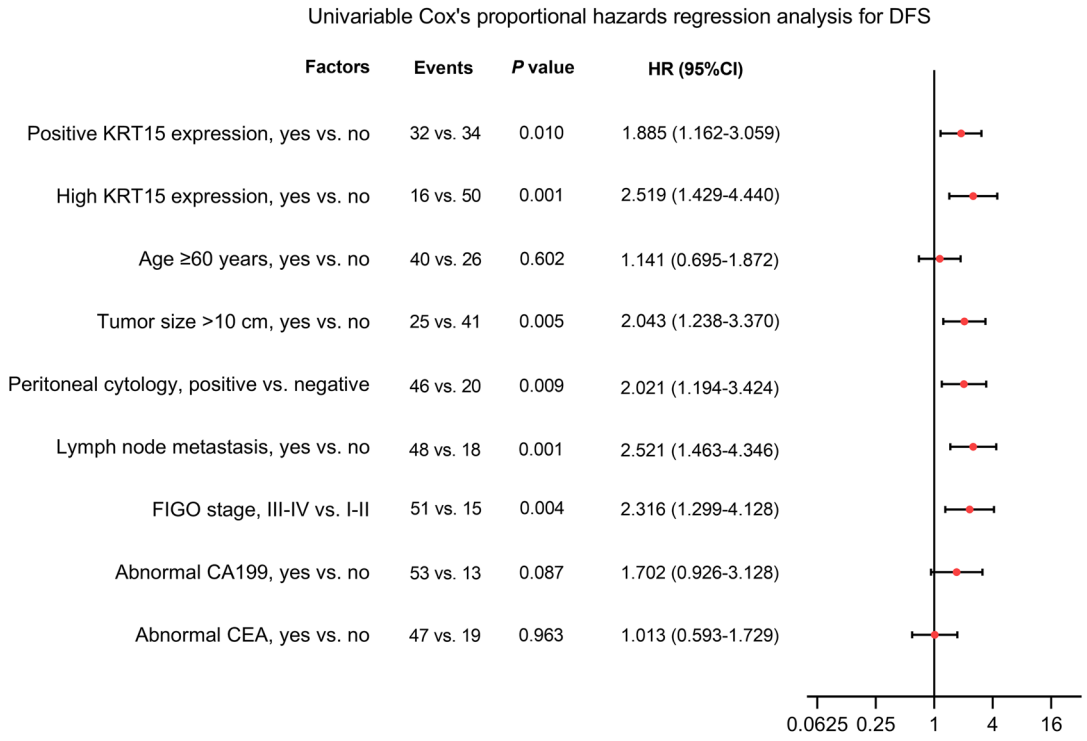
Fig. 3 DFS and OS were shorter in EOC patients with positive (versus negative) and high (versus low or no) KRT15 expression. Comparison of DFS in EOC patients with positive versus negative KRT15 expression (**A**) and in patients with high versus low or no KRT15 expression (**B**). Comparison of OS in EOC patients with positive versus negative KRT15 expression (**C**) and in patients with high versus low or no KRT15 expression (**D**)

Despite the aforementioned findings, there were several limitations in the present study: Firstly, this study was conducted retrospectively, hence, the confounding factors were hard to avoid. Secondly, selective bias was inevitable in this single center study. Thirdly, all patients in this study were post-operative EOC patients, and the prognostic value of KRT15 in metastasis EOC patients required further exploration.

5 Conclusions

In summary, KRT15 expression is generally insufficient in EOC tissues, whereas its expression is positively associated with lymph node metastasis, and its high expression can well predict dismal DFS and OS in EOC patients who undergo tumor resection.

A



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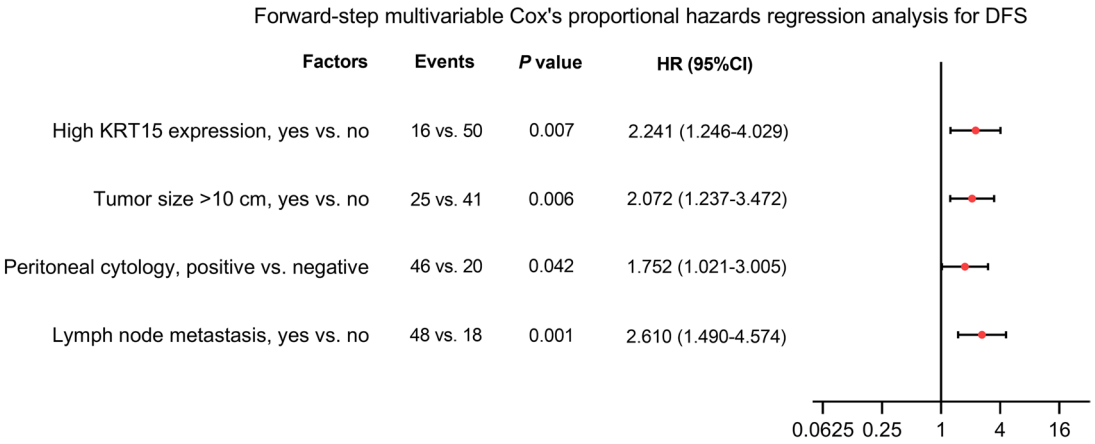

Fig. 4 High KRT15 expression was independently related to poor DFS of EOC patients. Related factors of DFS by univariable Cox regression analysis (**A**) and independent factors of DFS by multivariable Cox regression analysis (**B**) in EOC patients

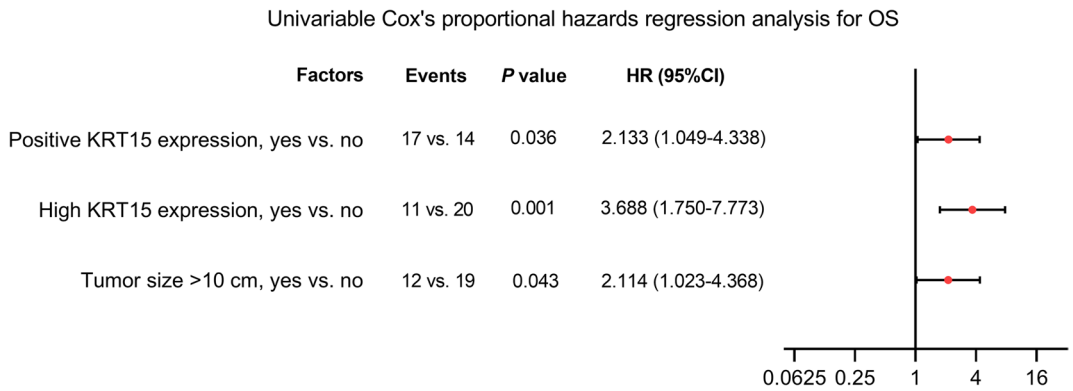

Fig. 5 Related factors of OS by univariable Cox regression analysis in EOC patients

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Author contributions Xuqin Feng: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing. Qian Wang: Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Writing - original draft, Writing—review & editing.

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Data availability The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate The Ethics Committee of The First Affiliated Hospital of Yangtze University approved the study. The study was carried out following the guidelines of the Ethics Committee. All patients or direct relatives provided the informed consent.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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