Observational Study

Medicine

OPEN

Upregulated keratin 15 links to the occurrence of lymphovascular invasion, stromal cervical invasion as well as unfavorable survival profile in endometrial cancer patients

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Abstract

Keratin 15 (KRT15) overexpression links with tumor initiation, metastasis, and poor survival in several solid carcinomas. While its clinical relevance is scarcely reported in endometrial cancer (EC). Therefore, the current study aimed to investigate the abnormal expression of KRT15 and its correlation with clinical characteristics, survival in EC patients.

Totally, 135 surgical EC patients were enrolled. KRT15 protein expression in formalin-fixed and paraffin-embedded tumor and adjuvant tissues was detected by immunohistochemical staining; meanwhile, KRT15 mRNA expression in fresh-frozen tumor and adjacent tissues was detected by reverse transcription-quantitative polymerase chain reaction.

KRT15 protein and mRNA expressions were higher in tumor tissue compared with adjacent tissue (both $P < .001$). Elevated KRT15 protein expression was correlated with the occurrence of lymphovascular invasion ($P = .010$) and more advanced International Federation of Gynecology and Obstetrics stage ($P = .018$); meanwhile, elevated KRT15 mRNA expression was linked with more advanced International Federation of Gynecology and Obstetrics stage ($P = .038$) and marginally associated with the occurrence of stromal cervical invasion ($P = .052$). Besides, KRT15 protein and mRNA expressions were not correlated with other clinical features (all $P > .05$). KRT15 protein high was marginally correlated with poor accumulating disease-free survival (DFS) ($P = .091$) and overall survival (OS) ($P = .059$); meanwhile, the correlation of KRT15 mRNA expression with accumulating DFS ($P = .212$) and OS ($P = .092$) was even weaker. However, multivariate Cox's regressions showed that tumor KRT15 protein (high vs low) was independently correlated with poor DFS ($P = .045$) and OS ($P = .043$).

KRT15 is abnormally increased in EC tissue, meanwhile, its upregulation links to the occurrence of lymphovascular invasion, stromal cervical invasion, and poor prognosis in EC patients.

Abbreviations: DFS = disease-free survival, EC = endometrial cancer, KRT15 = keratin 15, OS = overall survival, ROC = receiver operating characteristic, RT-qPCR = reverse transcription-quantitative polymerase chain reaction.

Keywords: disease-free survival, endometrial carcinoma, keratin 15, overall survival, tumor invasion

1. Introduction

Endometrial cancer (EC) is one of the most frequent malignancies and the fourth leading cause of cancer-related deaths in women worldwide in 2020.[1–4] Benefiting from the continuous improvement of the diagnosis and treatment for EC, most of them are diagnosed in the early stage and have a relatively favorable outcome (with a 5-year survival rate of 95%).[5] However, for those who are diagnosed in the advanced stage, the 5-year survival rate is still unsatisfying, which is mainly due to the occurrence of metastasis and increased risk of recurrence or rapid progression.[6–9] Hence, it is vital to discover a few novel indicators for predicting the prognosis of EC, which might help to optimize the treatment of EC patients and therefore improve their survival profile.

Keratin 15 (KRT15) is a type I keratin expressed in the human basal layer and stratified epidermis.[10,11] Interestingly, KRT15 exhibits to be cancer-promoting keratin.[11–15] For instance, 1 study illustrates that KRT15 induces tumor initiation and enhances the resistance to radiotherapy in mouse intestinal cancer models.[11] Besides, a clinical study shows that upregulated KRT15 is correlated with poor differentiation, more advanced clinical stage, and occurrence of lymph node metastasis in colorectal cancer patients.[12] Another 2 studies also exhibit that KRT15 overexpression is associated with tumor metastasis and poor prognosis

HY and AL contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

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How to cite this article: Yang H, Li A, Li A, Zhao F, Zhang T. Upregulated keratin 15 links to the occurrence of lymphovascular invasion, stromal cervical invasion as well as unfavorable survival profile in endometrial cancer patients. Medicine 2022;101:29(e29686).

Received: 24 January 2022 / Received in final form: 30 April 2022 / Accepted: 12 May 2022

http://dx.doi.org/10.1097/MD.0000000000029686

in breast cancer patients.[14,15] However, its clinical relevance in EC cancer patients remains elusive; hence, the current study aimed to investigate the KRT15 dysregulation and its correlation with clinical features and survival profile in EC patients.

2. Methods

2.1. Patients and specimens

This study retrospectively analyzed 135 EC patients treated by surgical excision between January 2016 and December 2020. The eligible patients satisfied the following criteria: histopathological diagnosis of EC; age >18 years; received surgical excision; surgically removed tumor and adjacent tissues were available; clinicopathologic features and follow-up documents were available; and no history of other cancers except EC. The ethical approval was obtained from the Ethics Committee. Formalin-fixed and paraffin-embedded specimen of each patient was collected for immunohistochemical (IHC) assay; besides, 76 fresh-frozen tumor and adjacent tissues were also acquired for reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay.

2.2. Data collection

For study analysis, the clinical characteristics were abstracted from patients' medical documents, and the follow-up data of patients were also acquired for survival analysis including disease-free survival (DFS) and overall survival (OS). The last follow-up date was April 30, 2021, and the median follow-up duration was 32 months (range: 7–59 months).

2.3. KRT15 detection by IHC assay

IHC staining was implemented to detect KRT15 protein expression in formalin-fixed and paraffin-embedded tissue. Cytokeratin 15 polyclonal antibody (1:1,000 dilution, Invitrogen, Carlsbad, CA) and goat anti-rabbit IgG (H+L) secondary antibody (1:4,000, dilution, Invitrogen, Carlsbad, CA) were used as primary antibody and secondary antibody, respectively. The diaminobenzidine and hematoxylin were applied for staining and counterstaining. Finally, the KRT15 protein expression was scored according to the IHC staining intensity and density.[16] In brief, the staining density was scored based on proportion of positively stained cells and as follows: 0 points for 0%, 1 point for 1% to 25%, 2 points for 26% to 50%, 3 points for 51% to 75%, and 4 points for 76% to 100%; accordingly, the staining intensity was scored as 0 points for no staining, 1 point for faint yellow, 2 points for pale brown, and 3 points for dark brown. The IHC score was gendered by multiplying the 2 scores. The IHC score ≤3 points was considered as KRT15 protein low expression; correspondingly, the IHC score >3 points was considered as KRT15 protein high expression.

2.4. KRT15 mRNA detection by RT-qPCR assay

Total mRNA was extracted from tumor tissue as well as adjacent tissue using GenElute ™ Total RNA Purification Kit (Sigma-Aldrich, Burlington, MA). Besides, reverse transcription was applied by QuantiTect Rev. Transcription Kit (Bio-Rad, Hercules, CA); meanwhile, qPCR was conducted using Terra™ qPCR Direct SYBR® Premix (Takara, Dalian, Liaoning, China). The primer took a previous study for reference[12]; besides, the KRT15 mRNA expression was categorized as low expression and high expression based on the median expression in the tumor tissue.

2.5. KRT15 protein detection by Western blot assay

Tumor tissue as well as adjacent tissue were lysed in Radio Immunoprecipitation Assay (RIPA; Beyotime, China) containing 1% protease inhibitor cocktail (Beyotime, China) for protein extraction, whose quantification was subsequently performed using bicinchoninic acid (BCA) quantification kit (Beyotime, China). Then, 4% to 20% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) precast gels (Beyotime, China) were applied to separate the thermal denatured protein, and the separated protein was transferred into polyvinylidene fluoride membrane (Beyotime, China), which was then blocked using 5% bovine serum albumin (BSA) for 1.5 hours at 37°C and incubated with KRT15 antibody (1:1000, Abcam, USA) overnight at 4°C. Followed by that, secondary antibody (1:10,000, Abcam, USA) was used to incubate the membranes for 1 hour at 37°C. Finally, ECL Plus Kit (Yeason, China) was used for chemiluminescence.

2.6. Statistical analysis

Data analysis and figure construction were completed using SPSS 26.0 (IBM Corp., Armonk, NY) and GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, CA). KRT15 expression difference was analyzed using Wilcoxon signed-rank test or Wilcoxon rank-sum test. The value of KRT15 expression in differentiating different tissues was estimated by receiver operating characteristic curve. Correlation between ordered variables were evaluated by Spearman's test. DFS and OS were estimated by Kaplan–Meier method and analyzed by log-rank test. Variables affecting prognosis were analyzed using Cox's proportional hazard model regression analysis. Statistical significance was set as a P value of $<.05$; marginal significance was set as $.05 \leq P < .1$.

3. Results

3.1. Characteristics of EC patients

The age was 60.1 ± 9.2 years in EC patients. Among whom, 18 (13.3%) EC patients were premenopause and 117 (86.7%) were postmenopause. Moreover, there were 37 (27.4%) and 66 (48.9%) patients with diabetes mellitus and hypertension, respectively. In regards to histological subtype, there were 99 (73.3%), 10 (7.4%), 18 (13.3%), and 8 (5.9%) patients with EC G1/G2, EC G3, serous carcinoma, and clear cell carcinoma, respectively. Besides, there were 54 (40.0%) patients with myometrial invasion ≥1/2 (50%). In terms of International Federation of Gynecology and Obstetrics (FIGO) stage, 81 (60.0%), 16 (11.9%), 27 (20.0%), and 11 (8.1%) patients were diagnosed as stage I, stage II, stage III, and stage IV, respectively. More detailed information is listed in **Table 1**.

3.2. Protein and mRNA expressions of KRT15

The IHC stain examples of KRT15 protein expression in tumor tissue and adjacent tissue (**Fig. 1A**). In detail, KRT15 protein expression was higher in tumor tissue compared with adjacent tissue (median [interquartile range]: 4.0 [3.0–8.0] vs 2.0 [2.0–4.0], $Z = -7.503$, $P < .001$; **Fig. 1B**), meanwhile receiver operating characteristic analysis disclosed that KRT15 protein expression exhibited a good capability in distinguishing tumor tissue from adjacent tissue (area under curve: 0.757; 95% confidence interval: 0.700–0.815; **Fig. 1C**). Besides, KRT15 mRNA expression was measured by RT-qPCR, which was higher in tumor tissue compared with adjacent tissue (median [interquartile range]: 2.555 [1.728–4.343] vs 0.985 [0.740–1.480], $Z = -8.597$, $P < .001$; **Fig. 1D**) as well; meanwhile, KRT15 mRNA expression exhibited an excellent capability in distinguishing tumor tissue from adjacent tissue (area under curve: 0.904; 95% confidence interval: 0.858–0.950; **Fig. 1E**).

3.3. Association of KRT15 expression with clinical features

Elevated KRT15 protein expression was correlated with the occurrence of lymphovascular invasion ($Z = -2.584$, $P = .010$) and more

Table 1

Characteristics of EC patients.

Items	EC patients (N = 135)
Age (yr), mean ± SD	60.1 ± 9.2
Menopausal status, n (%)	
Premenopause	18 (13.3)
Postmenopause	117 (86.7)
DM, n (%)	
No	98 (72.6)
Yes	37 (27.4)
Hypertension, n (%)	
No	69 (51.1)
Yes	66 (48.9)
Histological subtype, n (%)	
Endometrioid carcinoma G1/G2	99 (73.3)
Endometrioid carcinoma G3	10 (7.4)
Serous carcinoma	18 (13.3)
Clear cell carcinoma	8 (5.9)
Myometrial invasion ≥1/2 (50%), n (%)	
No	81 (60.0)
Yes	54 (40.0)
Cervical invasion, n (%)	
None or epithelial	101 (74.8)
Stromal	34 (25.2)
Lymphovascular invasion, n (%)	
No	97 (71.9)
Yes	38 (28.1)
FIGO stage, n (%)	
Stage I	81 (60.0)
Stage II	16 (11.9)
Stage III	27 (20.0)
Stage IV	11 (8.1)

DM = diabetes mellitus, EC = endometrial carcinoma, FIGO = International Federation of Gynecology and Obstetrics, SD = standard deviation.

advanced FIGO stage (r_s = 0.204, P = .018); meanwhile, increased KRT15 mRNA expression was linked with more advanced FIGO stage (r_s = 0.239, P = .038) and marginally associated with the occurrence of stromal cervical invasion (Z = –1.943, P = .052), but they were not related to other tumor features (**Fig. 2A–J**). However, KRT15 protein and mRNA expression were not correlated with any patients' basic features (all P > .05; **Table 2**).

3.4. Correlation of KRT15 expression with survival profile

KRT15 protein high expression was marginally correlated with poor accumulating DFS (χ^2 = 2.865, P = .091; **Fig. 3A**) and OS (χ^2 = 3.573, P = .059; **Fig. 3B**). Besides, KRT15 mRNA high expression was not linked with accumulating DFS (χ^2 = 1.561, P = .212; **Fig. 3C**), but marginally related to reduced OS (χ^2 = 2.835, P = .092; **Fig. 3D**).

Furthermore, the multivariate Cox's regressions for DFS showed that tumor KRT15 protein (high vs low; hazard ratio [HR] = 2.824, P = .045), age (≥60 vs <60 years; HR = 5.597, P = .002), and myometrial invasion ≥1/2 (50%; yes vs no; HR = 3.701, P = .005) were independently correlated with poor DFS (**Table 3**). Additionally, tumor KRT15 protein (high vs low; HR = 4.758, P = .043), age (≥60 vs <60 years; HR = 14.903, P = .010), and myometrial invasion ≥1/2 (50%; yes vs no; HR = 4.074, P = .020) were independently correlated with unfavorable OS.

3.5. KRT15 protein expression (detected by Western blot) and its association with survival profile

The examples of KRT15 protein expression (evaluated by Western blot [WB] assay) in tumor tissue and adjacent tissue were shown (Figure 1A, Supplemental Digital Content,

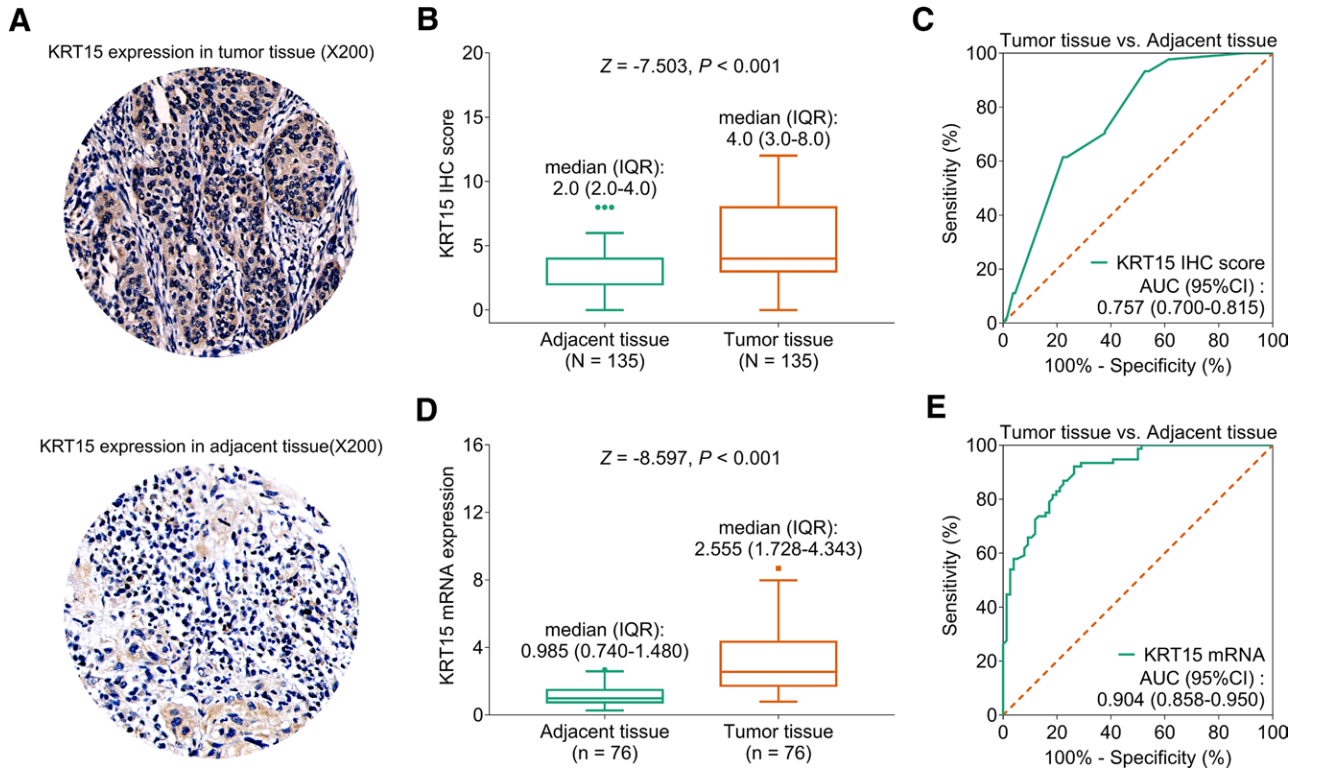

Figure 1. KRT15 expression was higher in tumor tissue than adjacent tissue. KRT15 protein expression detected by IHC assay (A); comparison of KRT15 protein expression between tumor tissue and adjacent tissue (B); ROC curve of KRT15 protein expression in distinguishing tumor tissue from adjacent tissue (C); comparison of KRT15 mRNA expression between tumor tissue and adjacent tissue (D); ROC curve of KRT15 mRNA expression in distinguishing tumor tissue from adjacent tissue (E). IHC = immunohistochemical, KRT15 = keratin 15, ROC = receiver operating characteristic.

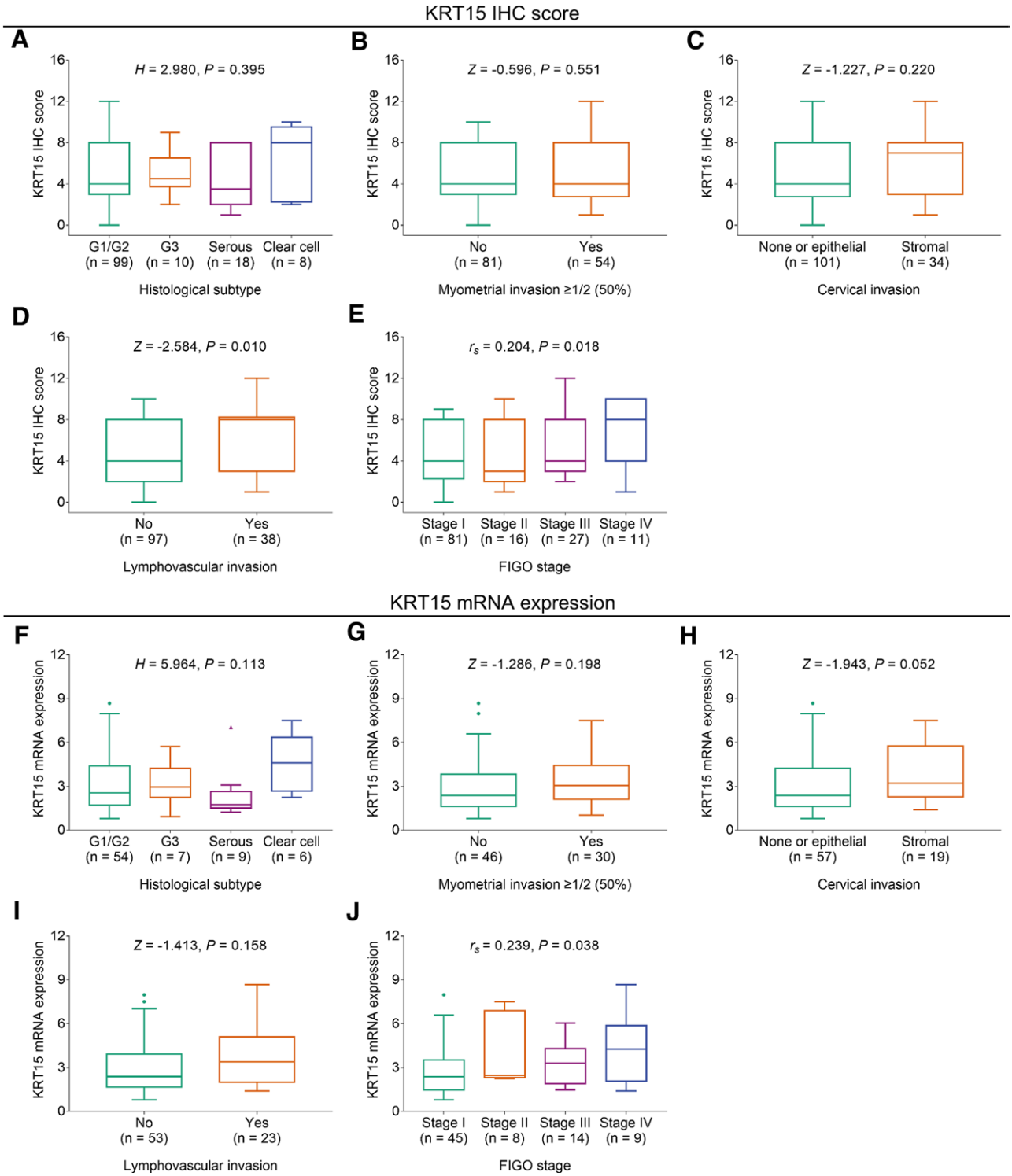

Figure 2. KRT15 overexpression linked with cervical invasion, lymphovascular invasion, and higher FIGO stage. Association of KRT15 protein expression with histological subtype (A), myometrial invasion (B), cervical invasion (C), lymphovascular invasion (D), and FIGO stage (E); Association of KRT15 mRNA expression with histological subtype (F), myometrial invasion (G), cervical invasion (H), lymphovascular invasion (I), and FIGO stage (J). FIGO = International Federation of Gynecology and Obstetrics, KRT15 = keratin 15.

http://links.lww.com/MD/G936). KRT15 protein expression (detected by WB) was elevated in tumor tissue than that in adjacent tissue in EC patients ($Z = -5.944$, $P < .001$, Figure 1B, Supplemental Digital Content, http://links.lww.com/MD/G936). Furthermore, KRT15 protein expression (detected by WB) was not linked with DFS ($\chi^2 = 2.186$, $P = .139$, Figure 1C, Supplemental Digital Content, http://links.lww.com/MD/G936) or OS ($\chi^2 = 1.254$, $P = .263$, Figure 1D, Supplemental Digital Content, http://links.lww.com/MD/G936).

4. Discussion

The abnormal expression of KRT15 is observed in a series of solid carcinomas, in detail, 1 study discloses that KRT15 is highly

Table 2

Correlation of tumor KRT15 expression with basic features.

	KRT15 IHC score				KRT15 mRNA expression			
Items	**N**	**Median (IQR)**	**Statistic (Z)**	***P* value**	**n**	**Median (IQR)**	**Statistic (Z)**	***P* value**
Age (yr)			−0.594	.552			−1.020	.308
< 60	63	4.0 (3.0–8.0)			30	2.395 (1.585–3.583)		
≥60	72	4.0 (3.0–8.0)			46	2.765 (1.973–4.530)		
Menopausal status			−0.576	.565			−0.914	.361
Premenopause	18	5.0 (2.9–8.3)			10	3.090 (1.668–5.993)		
Postmenopause	117	4.0 (3.0–8.0)			66	2.460 (1.743–4.260)		
DM, n (%)			−0.369	.712			−0.767	.443
No	98	4.0 (3.0–8.0)			55	2.390 (1.710–4.260)		
Yes	37	4.0 (2.0–8.0)			21	3.090 (1.980–4.410)		
Hypertension, n (%)			−0.745	.456			−0.493	.622
No	69	4.0 (3.0–8.0)			38	2.680 (1.675–4.900)		
Yes	66	4.0 (2.5–8.0)			38	2.440 (1.930–3.718)		

DM = diabetes mellitus, IHC = immunohistochemistry, IQR = interquartile range, KRT15 = keratin 15.

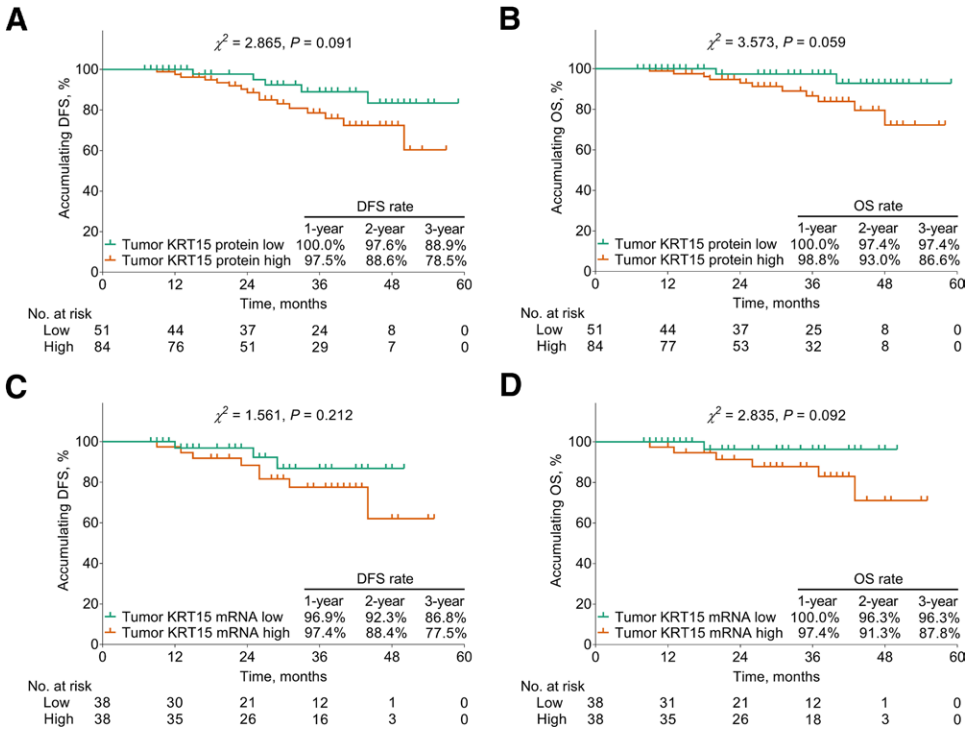

Figure 3. KRT15 overexpression marginally linked with unsatisfying survival profile. Correlation of KRT15 protein expression with accumulating DFS (A) and OS (B). Correlation of KRT15 mRNA expression with accumulating DFS (C) and OS (D). DFS = disease-free survival, KRT15 = keratin 15.

expressed in crypt cells of intestinal cancer mice.[11] Another study illuminates that KRT15 is overexpressed in carcinoma tissue compared with normal tissue from colorectal cancer patients.[12] Differently, it is illustrated that KRT15 is downregulated in carcinoma tissue compared with normal tissue from breast cancer patients.[14,15,17] KRT15 expression discloses an opposite trend in breast cancer, which might be explained by that: The apoptosis and differentiation of KRT15 would be influenced by endocrine status, hence, we hypothesize that KRT15 expression in breast cancer might be affected by the hormonal environment (such as estrogen, progesterone, etc)[18,19]; whereas, this speculation needs further investigation in the in vivo and in vitro studies. In the current study, it was discovered that KRT15 was higher in tumor tissue compared with adjacent tissue; meanwhile, it exhibited an acceptable capability in distinguishing tumor tissue from adjacent tissue. A possible explanation could be that KRT15, which serves as a tumor-initiating protein, might reflect the speed of cell proliferation; moreover, the malignant proliferation speed of EC cells is thought to be faster than that in the normal cells; thus, KRT15 is overexpressed in tumor tissues.[20–22]

Tumor KRT15 is also reported to reflect tumor features such as poor differentiation, metastasis, and advanced clinical stages in several solid carcinomas.[13–15] For example, a previous research discloses that upregulated KRT15 is linked with poor differentiation, the occurrence of lymph node metastasis, and a more advanced T stage in colorectal cancer.[12] Besides, another study reveals that KRT15 overexpression is associated with tumor metastasis in breast cancer patients.[17] In the present study, KRT15 protein expression was correlated with the occurrence of lymphovascular invasion and more advanced FIGO stage; meanwhile, KRT15 mRNA expression was correlated with the more advanced FIGO stage and marginally associated with the occurrence of stromal cervical invasion. Possible explanations could be that: KRT15 upregulation is associated with enhanced cancer stem cell property which exhibits a strong infiltration capacity; thus, KRT15

Table 3

Multivariate Cox's regressions on DFS and OS.

Variables	*P* value	HR	95%CI	
			Lower	Upper
DFS				
Tumor KRT15 protein (high vs low)	.045	2.824	1.022	7.800
Age (≥60 vs <60 yr)	.002	5.597	1.870	16.750
Myometrial invasion ≥1/2 (50%) (yes vs no)	.005	3.701	1.481	9.244
OS				
Tumor KRT15 protein (high vs low)	.043	4.758	1.047	21.625
Age (≥60 yvs <60 yr)	.010	14.903	1.927	115.281
Myometrial invasion ≥1/2 (50%) (yes vs no)	.020	4.074	1.248	13.296

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, KRT15 = keratin 15, OS = overall survival.

overexpression is linked with the occurrence of lymphovascular invasion and stromal cervical invasion in EC patients. KRT15 overexpression is linked with immune-cell infiltration of NK cells, mast cells, and B cells whose infiltration might enhance tumor progression in EC.[14] Thus, KRT15 overexpression is linked with the occurrence of lymphovascular invasion in EC patients. KRT15 upregulation is linked with progressed disease reflected by the occurrence of lymphovascular invasion and stromal cervical invasion; thus, KRT15 upregulation is correlated with higher FIGO stage.[23,24]

Apart from the above-mentioned relevance of KRT15 with clinical features, its upregulation also links with an unsatisfying survival profile in breast cancer and non–small cell lung cancer.[17,25] Herein, the KRT15 overexpression was marginally correlated with accumulating DFS and OS in EC patients, which was estimated by Kaplan–Meier method and analyzed by log-rank test, whereas further adjusted multivariate Cox's regressions showed that tumor KRT15 protein (high vs low) was independently correlated with poor DFS and OS. Possible explanations could be that KRT15 overexpression is linked with enhanced cancer stem cell properties and therefore lined with a higher recurrence rate; thus, KRT15 overexpression is correlated with poor survival indexes. The relevance between KRT15 and survival profile (estimated by the Kaplan–Meier method and analyzed by log-rank test) shows that KRT15 is not a prognostic indicator for EC, which would probably be due to the shelter of confounding factors.

However, despite the innovation in the current study, some limitations still existed: the current study was single-center research; hence, multicenter studies were needed. The sample size was relatively small in the present research, which might potentially result in a less strong statistical power for analysis. The follow-up assessment of the current study was comparatively short, which needed to be prolonged. The expression of other keratin members (such as K8, K17, K18, and K19) deserved to detect in EC patients in further studies.

In conclusion, KRT15 is abnormally increased in EC tissue; meanwhile, its upregulation links to the occurrence of lymphovascular invasion, stromal cervical invasion, and poor prognosis in EC patients.

Author contributions

Hongxiang Yang: formal analysis, conceptualization, resources, writing – original draft; Aijing Li: formal analysis, conceptualization, resources, writing – original draft; Aili Li: formal analysis, conceptualization, supervision,writing – review & editing; Fei Zhao: data curation, writing – review & editing, project administration; Tongyan Zhang: data curation, writing – original draft, investigation.

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