Research Article

Prognostic Value and Immune-Infiltration Pattern of KIF4A in Patients with Endometrial Carcinoma

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Background. With the development of sequencing technology, an increasing number of biomarkers has been identified in endometrial carcinoma (EC). However, there have been few comprehensive analyses of the KIF4A gene in patients with EC.

Methods. Based on raw data in public databases, the KIF4A gene and protein expression in EC were validated. Logistic regression analysis was conducted to analyze the correlations between clinical characteristics and the KIF4A expression. Kaplan-Meier analysis was used to explore the difference in survival in clinical subgroups. Meanwhile, we used meta-analysis in multiple datasets to investigate the prognostic value of KIF4A. In addition, Cox regression analysis was used to confirm the independent prognostic value of KIF4A, and we constructed a nomogram based on KIF4A expression. Subsequently, we used ESTIMATE and ssGSEA algorithms to excavate the correlation between KIF4A, tumour-infiltrating immune cells, and related gene markers of immune cells. Moreover, the potential biological functions of KIF4A were investigated by gene function annotation. Finally, we identified the hub genes interacting with KIF4A by constructing a protein-protein interaction (PPI) network and screening differential genes (DEGs).

Results. In the pan-cancer analysis, KIF4A was upregulated in most tumors (21/33). Similarly, the overexpression of KIF4A in EC patients was confirmed in the TCGA cohort, the GEO cohort, and immunohistochemistry. In addition, upregulated KIF4A is associated with age, survival status, grade, FIGO stage, histological type, tumour invasion, and TCGA molecular subtypes (p < 0.05). KIF4A overexpression was correlated with the grade, histological type, and pathological stage according to logistic regression analysis (p < 0.05). Meanwhile, survival analysis and meta-analysis revealed that KIF4A was associated with a poor prognosis and acted as an independent prognostic marker in EC patients (p < 0.05). KIF4A is associated to immune response and may have a function in controlling immune cell infiltration in EC (20/24, p < 0.05). This is noteworthy given that gene enrichment analysis suggested KIF4A may be involved in the neuroactive ligand-receptor interaction pathway, etc. Finally, we identified transcription factors which have a potential interaction with KIF4A. Conclusion. We provided robust evidences that KIF4A is an indicator of poor prognosis and a potential target for immunotherapy in patients with EC.

1. Introduction

Endometrial cancer (EC) is a reproductive system malignancy that affects women’s health, with over 200,000 new cases diagnosed each year worldwide. It is worth noting that EC patients are becoming younger [1]. In 2020, the National Comprehensive Cancer Network (NCCN) included TCGA molecular subtypes within its guidelines, and it is recommended for predicting prognosis and guiding treatment [2]. Therefore, it is necessary to explore further biomarkers of targeted therapies for EC based on the TCGA database.

KIF4A belongs to the kinesin superfamily, and its location and function in the nucleus change depending on the cell cycle stage [3]. KIF4A is closely related to the formation of a spindle during mitosis and the completion of cytoplasmic division [4] and intracellular transport of chemicals.
The expression of KIF4A

(a)

(b)

(c)

Figure 1: Continued.
because DNA damage can lead to abnormal cell proliferation and differentiation, which ultimately promotes tumour formation [6].

KIF4A is involved in the DNA damage repair pathway [6], so we speculate that KIF4A is closely related to the occurrence and prognosis of tumors. Numerous investigations on the biological process of KIF4A in ovarian cancer [7], cholangiocarcinoma [8], esophageal cancer [9], and bladder cancer [10] have been conducted. To our knowledge, only one study has focused on the role of KIF4A as the lncRNA LINC01123 target-gene in EC [11]. However, the intricate regulatory mechanism and prognostic value of KIF4A in EC is unclear.

In this study, we selected several public databases to validate the expression of KIF4A in EC patients. In the meantime, we used meta-analysis and Kaplan-Meier analysis to investigate its prognostic value in different clinical subgroups and demonstrated the independent prognostic value. We developed a visual prognostic model (nomogram) based on KIF4A expression. In addition, we explored the differences in immune infiltration between EC patients with different expression levels of KIF4A. Notably, the PPI network predicted a potential gene (transcription factor NFIB) interacting with KIF4A.

2. Materials and Methods

2.1. Datasets. Following the method of reference [12], we downloaded RNA-sequence data (level-3 HTseq-FPKM) from the Pan-Cancer Project in The Cancer Genome Atlas (TCGA) database. In addition, the Uterine Corpus Endometrial Carcinoma (UCEC) RNA-sequence data was downloaded from the TCGA database to perform KIF4A difference analysis of paired (22 pairs) and unpaired (552 endometrial cancer tissue and 35 adjacent normal endometrial tissue). External validation of GSE17025 datasets (92 endometrial cancer tissue and 12 adjacent normal endometrial tissue) was downloaded from the GEO database. The expression of KIF4A protein was excavated from the Human Protein Atlas (HPA) database.

2.2. Prognosis Analysis. Clinical data were extracted from the TCGA database. FIGO stage, age, BMI, histological type, histologic grade, tumor invasion, and residual tumor are included in the clinical features; survival data include Overall Survival (OS), Disease-Specific Survival (DSS), and Progress-Free Interval (PFI), as reported in Table S1. We determined the median KIF4A expression in EC patients and utilized this value to create “high-KIF4A” and “low-KIF4A” groups. Kaplan-Meier survival analysis and the log-rank test indicate that there are differences in survival outcomes (OS, DSS, and PFI) between two groups. Additionally, univariate and multivariate Cox regression analyses were used to identify independent prognostic variables. Additionally, univariate and multivariate Cox regression analyses were used to identify independent prognostic variables. Additionally, we utilized the R software package “rms” to generate a nomogram to visualize the prognostic value of KIF4A. The ROC curve and calibration curve were used to examine the distinction and calibration.

2.3. Enrichment Analysis. The differentially expressed genes (DEGs) in KIF4A-high samples and KIF4A-low samples were screened using the “deseq2” package in R software. The thresholds were set to |log2(FC)| >2 and p.adj < 0.05. Moreover, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed using related packages. The thresholds were set to p.adj < 0.05 and qvalue < 0.2.
The expression of KIF4A
log2 (FPKM+1)

Age

BMI

Clinical stage

Histological type

Histologic grade

Tumor invasion (%)

Figure 2: Continued.
2.4. Immune Analysis. The immune infiltration algorithm used in this study was ssGSEA. In addition, we used ESTIMATE algorithm to speculate the infiltration of stromal and immune cells in EC tissues from the TCGA database. We combined the above two algorithms to estimate the relationship between the expression of KIF4A and immune infiltration, including immune score, stromal score, ESTIMATE score, and immune cell correlation.

2.5. Construction of PPI Network. In order to screen the potentially interacting molecules with KIF4A in EC patients, the PPI network was constructed by using STRING and Cytoscape software. We retained the top 50 genes with the interaction relationship with KIF4A for the construction of the PPI network.

2.6. Statistical Analysis. All statistical analyses were performed using the R software (v.3.6.3). Detailed statistical methods are covered in the bioinformatics method section. 

\[ p < 0.05 \] was considered statistically significant.

3. Result

3.1. KIF4A Expression in Pan-Cancer and EC Patients. Firstly, we identified the expression of KIF4A in various cancers and focused on EC. We found that there were significant differences in the expression of KIF4A in pan-cancer patients (21/33, \( p < 0.05 \)), as shown in Figure 1(a). Of note, KIF4A was upregulated in all gynecological tumors. In addition, we explored expression of KIF4A by combining normal endometrial tissue samples in the GTEx database, and the same results were found (\( p < 0.001 \), Figure 1(b)). Meanwhile, significant upregulation of KIF4A was also observed in paired samples (Figure 1(c)) and the GSE17025 cohort (Figure 1(d)). Not surprisingly, representative Immunohistochemical staining of KIF4A protein in the HPA database revealed a lower expression in normal samples (Figure 1(e)).

3.2. Identification of the Correlation between KIF4A Expression and Clinical Characteristics. Correlation analysis was performed between the KIF4A expression and corresponding clinical characteristics. As presented in Figure 2, the increased expression of KIF4A is remarkably related to multiple factors, including age (Figure 2(a)), FIGO stage (Figure 2(c)), histological type (Figure 2(e)), tumor invasion (Figure 2(f)), and OS status (Figure 2(h)) (\( p < 0.05 \)). Meanwhile, it should also be noted that the expression of KIF4A was not statistically correlated with the following clinical characteristics: BMI (Figure 2(b)) and tumor residual (Figure 2(h)). Furthermore, as shown in Table 1, using the median of KIF4A expression as the dependent variable, logistic regression analysis revealed that overexpression KIF4A was significant with the FIGO stage (advanced
Figure 3: Continued.
Low KIF4A
High

Overall survival
HR = 2.77 (1.49-5.15)
Log-rank $P = 0.01$

Clinical stage: stage I & stage II

KIF4A
Low
High

(f)

Age: < = 60

Overall survival
HR = 3.08 (1.35-7.02)
Log-rank $P = 0.03$

Histological type: Endometrioid

KIF4A
Low
High

(g)

Overall survival
HR = 1.88 (1.02-3.49)
Log-rank $P = 0.023$

Histological type: Mixed & Serous

KIF4A
Low
High

Figure 3: Continued.
Figure 3: Prognostic value of KIF4A in EC Patients. Kaplan-Meier survival analysis of (a) OS, (b) DSS, (c) PFI, and (d) ROC analysis for status (tumor or normal). Survival analysis of clinical subgroups, including (e) FIGO stage, (f) age, (g) histological type, (h) histologic grade, (i) venous invasion, and (j) BMI.
stage vs. early stage, \( p < 0.001 \), grade (G3 vs. G1 and G2, \( p < 0.001 \)) and histological type (mixed and serous vs. endometrioid, \( p < 0.001 \)).

### 3.3. Prognostic Value of KIF4A in EC Patients.

To further explore the prognostic value of KIF4A, we performed survival analysis of the clinical subgroup. Firstly, we calculated the median expression of KIF4A of EC patients, which is used to select “high-KIF4A” and “low-KIF4A” groups. Kaplan-Meier survival analysis and log-rank test were used to suggest the survival differences (OS, DSS, and PFI) in two groups. The results showed that the survival time of the high-expression group was significantly shorter than that of the low-expression group (OS, \( p = 0.0003 \), Figure 3(a); DFS, \( p = 0.006 \), Figure 3(b); PFI, \( p < 0.001 \), Figure 3(c)). In addition, we also analyzed the prediction value of KIF4A in status (tumor or normal), and the ROC curve results showed that KIF4A had a terrific predictive performance (AUC:0.978, Figure 3(d)). In the survival analysis of the clinical subgroups, the survival time of the high-KIF4A group was significantly shorter than that of the low-KIF4A group in the early group (\( p = 0.01 \), Figure 3(e)), elderly and none-elderly group (\( p = 0.012/0.03 \), Figure 3(f)), endometrioid group (\( p = 0.023 \), Figure 3(g)), tumor invasion (% < 50 group (\( p = 0.009 \), Figure 3(i)), and BMI > 30 group (\( p = 0.012 \), Figure 3(j)). Although there was no significant difference in survival time among the subgroups of the advanced stage group, mixed and serous group, grade subgroups (Figure 3(h)), tumor invasion (% ≥ 50 group, and BMI < 30 group, it is of concern.

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**Figure 4:** Meta-analysis of the prognostic value and comparison of TCGA molecular subtypes. (a) Meta-analysis of OS in EC patients. (b) Meta-analysis of PFS in EC patients. The relationship between KIF4A expression and degree of the lesion (c) and TCGA molecular subtypes (d).
### Table 1: HR (95% CI) and P values for various characteristics

| Characteristics       | HR (95% CI)           | P value |
|-----------------------|-----------------------|---------|
| KIF4A                 | 1.658 (1.396-2.510)   | 0.017   |
| FIGO stage            | 3.270 (2.145-4.984)   | < 0.001 |
| Age                   | 1.847 (1.160-2.940)   | 0.01    |
| Histological type     | 2.628 (1.746-3.957)   | < 0.001 |
| Grade                 | 3.281 (1.907-5.643)   | < 0.001 |
| Tumor invasion        | 2.813 (1.744-4.535)   | < 0.001 |
| Residual tumor        | 3.101 (1.768-5.440)   | < 0.001 |
| Surgical approach     | 1.409 (0.924-2.150)   | 0.111   |

### Table 2: HR (95% CI) and P values for various characteristics

| Characteristics       | HR (95% CI)           | P value |
|-----------------------|-----------------------|---------|
| KIF4A                 | 1.229 (1.123-1.650)   | 0.043   |
| FIGO stage            | 3.071 (1.607-5.868)   | < 0.001 |
| Age                   | 1.603 (0.828-3.105)   | 0.162   |
| Histological type     | 1.128 (0.579-2.196)   | 0.723   |
| Grade                 | 1.774 (0.848-3.711)   | 0.128   |
| Tumor invasion        | 1.339 (0.725-2.474)   | 0.351   |
| Residual tumor        | 2.142 (1.107-4.145)   | 0.024   |

### Figure 5: Continued.

- **Points**
  - Clinical stage
  - Residual tumor
  - KIF4A

- **Total points**

- **Linear predictor**
  - 1-year survival probability
  - 3-year survival probability
  - 4-year survival probability

**Figure 5:** Continued.
3.4. Meta-Analysis of the Prognostic Value and Comparison of TCGA Molecular Subtypes. To further illustrate the prognostic value of KIF4A and correlation with TCGA molecular subgroups, we performed meta-analysis of KIF4A by combining three datasets (TCGA, GSE106191, and GSE17015), where we used the random effects model. Among the results in the meta-analysis of OS, KIF4A was shown to be a high risk factor for survival in EC patients, HR = 1.60 (1.07-23.9), as shown in Figure 4(a). Meanwhile, the same results were shown in the meta-analysis of PFS, HR = 1.71 (1.11-3.00), as shown in Figure 4(b). We analyzed the correlation between KIF4A expression and cancer progression, and TCGA molecular subtypes in the GEO dataset. With the progression of tumor, the expression of KIF4A was upregulated (Figure 4(c), \( p < 0.05 \)). In addition, it is interesting to note that KIF4A expression is highest in CN-high (Figure 4(d), \( p < 0.05 \)).

3.5. Construction of Nomogram Based on KIF4A. The independent prognostic value of KIF4A in EC patients was investigated, in which univariate Cox analysis revealed that KIF4A was a high-risk factor (Figure 5(a)). Moreover, further multivariate Cox analysis showed that KIF4A, FIGO stage, and tumor residual were independently associated with OS, which may imply that KIF4A may be an independent prognostic predictor for EC patients (Figure 5(b)). Meanwhile, we combined significance factors in multivariate analysis to construct a visual prognostic model (Figure 5(c)). The ROC curve and calibration curve also showed that the model had better predictive value (Figures 5(d) and 5(e)).

3.6. Correlation between KIF4A Expression and Immune Infiltration in EC. In particular, infiltrating immune cells are an independent predictor of survival in patients with EC. Therefore, we explored the correlation between KIF4A and 24 immune cells, as well as the relationship between the expression of KIF4A mRNA and immune cells using the ssGSEA algorithm. Based on the median expression value of KIF4A, all EC patients were classified into high- and low-expression groups. The results showed that most of the cells were significantly different between groups except for aDC, B cell, DC, macrophages, Tem, Tgd, and Th1 cells (Figures 6(a)–6(c), \( p < 0.05 \)). Meanwhile, the results showed that KIF4A was correlated with most immune cells, except Th1 cells, aDC, macrophages, and B cells (Figure 6(d)). In addition, ESTIMATE analysis revealed that the low-KIF4A group had a higher immune and stromal score than the high-KIF4A group (Figures 6(e)–6(g)). Finally, Pearson analysis showed that KIF4A expression correlated with the expression of most immune cell marker genes (Table 2, \( p < 0.05 \)).

3.7. Analysis of the Potential Mechanisms of KIF4A. In order to explore the potential mechanism of KIF4A involvement, we performed gene enrichment analysis on all the DEGs from high- and low-risk groups (Figure 7(a)). Based on the results of the KEGG pathway analysis of DEGs, the genes were mainly enriched in neuroactive ligand-receptor interaction, metabolism of xenobiotics by cytochrome P450, etc. (Figure 7(b)). Based on the results of the GO enrichment analysis of DEGs, the genes were mainly enriched in complement activation, classical pathway, humoral immune response mediated by circulating immunoglobulin, complement activation, etc. (Figure 7(c)). In addition, we performed GSEA enrichment analysis of the above genes, and we show some of the results in Figures 7(d) and 7(e) and...
Figure 6: Continued.
Figure 6: Correlation between KIF4A expression and immune infiltration in EC. (a–c) Differential expression analysis of 24 immune cells in patients with different KIF4A expressions. (d) Pearson analysis of 24 immune cells and CRIP1 expression; comparison of stromal scores (e), immune scores (f), and ESTIMATE scores (g) based on the ESTIMATE tool. *p < 0.05, **p < 0.01, ***p < 0.001.
others in Table S2. GSEA showed that these genes may be associated with biological oxidations, etc.

3.8. A Prediction about Protein-Protein Interaction of KIF4A.

To identify potential interaction networks in the above 244 DEGs, we constructed a circular PPI network based on the STRING database and Cytoscape software (Figure 8(a)). Meanwhile, the heat map showed the top 20 genes of \(|\text{logFC}|\), and the correlation with KIF4A was shown on the right side of the heat map (Figure 8(b)). In addition, we performed topological analysis of the genes in the PPI network by Cytoscape, and finally, identified five hub genes (Figure 8(c)). Finally, we identified NFIB, which may be closely related to KIF4A (\(p < 0.001\)). Given that NFIB is a transcription factor, we speculated that the promoter of KIF4A has a potential NFIB site; however, this needs to be verified by future experiments.

4. Discussion

We conducted a detailed examination of KIF4A in EC in this study. We analyzed KIF4A’s genetic landscape across several datasets and discovered a strong association between KIF4A and clinicopathological variables. Simultaneously, several investigations established KIF4A’s remarkable prognostic potential. Additionally, we investigated the possible mechanism of KIF4A and its effect on immunological function. Finally, based on 244 DEGs, NFIB was the most critical transcription factor controlled upstream of KIF4A. However, to the best of our knowledge, the role of KIF4A in EC remains unknown.

Because of its adverse consequences, EC has gotten a lot of attention [2]. In recent decades, the global incidence has risen [1]. Immunotherapy has shown some promise in the treatment of a variety of cancers in recent research [13]. As a result, biomarkers discovered in this work, KIF4A can be utilized to assess treatment responsiveness and survival outcomes in EC patients. In addition, PPI networks have been extensively investigated, and its topology is frequently linked
Figure 7: Analysis of the potential mechanisms of KIF4A. (a) Volcano map of DEGs. (b) GO enrichment analysis. (c) KEGG enrichment analysis. (d, e) GSEA enrichment analysis.
Figure 8: Continued.
to diseases [14, 15]. Therefore, NFIB, a hub gene found in our study, may interact with KIF4A.

This study has several limitations. Firstly, our survival and KIF4A expression analyses were derived from public databases, mainly Caucasians. Therefore, the lack of clinical information from other ethnic groups may result in poor extrapolation. Second, no laboratory experiments were performed to validate the mechanism of KIF4A with NFIB. This also indicates that the role of KIF4A in EC is the focus of our future research. Finally, since the TCGA-EC cohort had relatively fewer stage III-IV samples than stage I-II, our conclusion may be more accurate in predicting early stage EC patients.

5. Conclusions

This study has identified some novel DEGs and pathways in EC. More specifically, KIF4A is a hub gene with the ability to promote EC progression and affect the immune microenvironment. We provide a potential transcription factor (NFIB) associated with KIF4A that can be used in subsequent studies. Our findings provide researchers with potential therapeutic targets for EC therapy.

Data Availability

The following information was supplied regarding data availability: data is available at the TCGA database (https://portal.gdc.cancer.gov/).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

X.S. and Z.Y. conceived and designed the study. S.L. and Z.Y. did the main experiments. S.L. analyzed and interpreted the data. X.S. was responsible for reagents and materials. X.S. drafted the article. Y.L. and S.L. revised the article critically. All authors had final approval of the submitted versions. Zhujuan yang and Xiaoqing Shen contributed equally to this work. 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.

Supplementary Materials

Supplementary 1. Table S1: KIF4A expression and clinical characteristics of EC patients in TCGA database (excluded unknown samples).

Supplementary 2. Table S2: results of GSEA analysis based on high- and low-risk groups.

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