Original Article

KLRB1 is a novel prognostic biomarker in endometrial cancer and is associated with immune infiltration

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Background: Endometrial cancer (EC) has the characteristics of high mortality and poor prognosis in the advanced stage, which seriously threatens women's health. Killer cell lectin-like receptor B1 (*KLRB1*) is a promising immune checkpoint of which the expression level can regulate the killing effect on tumor cells of the immune system, thereby affecting the survival and prognosis of tumor patients. However, it is still unclear whether *KLRB1* is associated with survival and prognosis in patients with EC. Therefore, our study focused on the relationship between *KLRB1* and immune cells to explore the role of *KLRB1* on the immune microenvironment, and to further explore its feasibility as a prognostic marker in EC.

Methods: In this study, The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases were used to analyze the messenger RNA (mRNA) expression level of *KLRB1* in normal endometrial and EC tissues. The University of Alabama at Birmingham Cancer data analysis Portal (UALCAN) database was used to determine the correlation between *KLRB1* mRNA expression and clinical features among the EC patients. *KLRB1* expression levels were investigated in the Tumor IMmune Estimation Resource (TIMER) database to reveal its relationship with immune cell infiltration of EC. Finally, using the R package clusterProfiler, enrichment analysis was performed on *KLRB1* to study its potential function.

Results: The results suggested that *KLRB1* expression varied in different tumor tissues, and the EC group had lower mRNA expression levels than did the control group. It was also found that patients with high expression of *KLRB1* had a better prognosis. According to further enrichment and immune infiltration analyses, *KLRB1* expression had a closed relationship with the level of infiltration of some immune cell types, such as B cells memory, eosinophils, and Tregs, among others.

Conclusions: *KLRB1* expression is associated with the infiltration of immune cells and can be used as a prognostic biomarker in EC.

Keywords: Endometrial cancer (EC); *KLRB1*; immune infiltration; prognostic biomarker

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Introduction

Endometrial cancer (EC) has the characteristics of high mortality and poor prognosis in the advanced stage, with 417,000 new diagnoses made globally in 2020 (1). Unfortunately, the number of patients diagnosed with EC continues to increase. Based on the best-fitting model, by 2030 there will be 42.13 new cases of EC annually for every 100,000 women (2). Although early detection of EC is ideal and some progress has been made in early treatment, the current reality is that the majority of clinically aggressive EC subtypes are usually diagnosed at an advanced stage, and female EC still has an increased mortality rate (3). In addition, advanced EC is predisposed to occur in 3–13% of cases and has a poor prognosis (4). Furthermore, women who are cured of EC still face a significant risk of cardiovascular death due to the mostly unrecognized and undertreated risk factors (5). To improve the risk stratification system and the quality of care for women with EC, the latest European (ESGO/ESTRO/ESP 2020) guidelines proposed a novel risk stratification model including The Cancer Genome Atlas (TCGA) molecular groups to assess the prognosis of EC and the role of the molecular subtypes of EC as prognostic factors independent from classic types (6,7). Although molecular signature-characterized studies are innovative and precise in diagnosing EC patient characteristics, they are complex and costly. Therefore, new biomarkers are needed to predict the EC prognosis and provide new targets for the treatment.

Highlight box

Key findings

- *KLRB1* expression is associated with the infiltration of immune cells and can be used as a prognostic biomarker in endometrial cancer (EC).

What is known and what is new?

- *KLRB1* is a promising immune checkpoint of which the expression level can regulate the killing effect of the immune system on tumor cells, thereby affecting the survival and prognosis of tumor patients.
- The results of our study suggested that the EC group had lower *KLRB1* mRNA expression levels than those of the control group. *KLRB1* also has close correlation with cancer stage, ethnicity, weight, histological subtypes, and immune infiltration. High expression of *KLRB1* was associated with a better prognosis.

What is the implication, and what should change now?

- *KLRB1* is a potential biomarker for EC prognosis.

Killer cell lectin-like receptor B1 (*KLRB1*) is a gene which encodes CD161 and is expressed on CD4 T cells, CD8 T cells, and natural killer (NK) cells (8). In general, *KLRB1* makes great contributions to lymphocyte differentiation (9). A previous study suggested that in most tumors, high expression of *KLRB1* can suppress tumor development, helping to improve the quality of life and extend the lifespan of patients (10). Besides, the role of *KLRB1* in lung adenocarcinoma, glioma, and colon cancer has been investigated, and the results have shown that the immune function of *KLRB1* is strongly associated with the development of those tumors (11-13). Another study also suggested that knockdown of *KLRB1* inhibits tumor cell growth in esophageal squamous cell carcinoma (14). Meanwhile, *KLRB1* can interact with LLT1 and actively participate in anti-tumor immune response in non-small cell lung cancer (15). Therefore, *KLRB1* is considered an indispensable gene in tumor immunomodulation. However, little research has been conducted on *KLRB1* in patients with EC.

In this study, pan-cancer analysis of *KLRB1* expression was performed. Furthermore, the expression of *KLRB1* in normal endometrium and EC tissues was investigated using TCGA and the Gene Expression Omnibus (GEO) databases. We also analyzed the relationship between *KLRB1* expression levels and various clinical features of EC patients by using the University of Alabama at Birmingham Cancer data analysis Portal (UALCAN) database. Finally, we focused on the relationship between *KLRB1* and immune cells to explore the role of *KLRB1* on the tumor immune microenvironment (TIME) and to further explore its feasibility as a prognostic marker in EC. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-697/rc).

Methods

Materials

The data used in this study were all from public databases on the Internet. We followed the methods of the previous study to conduct the data analysis (16). The following are links to the website of each database that we used: TCGA database (https://cancergenome.nih.gov/), Tumor IMmune Estimation Resource (TIMER) database (http://timer.cistrome.org/), GEO database (https://www.ncbi.nlm.nih.gov/), The Human Protein Atlas (HPA) database

(https://www.proteinatlas.org/), and UALCAN database (http://ualcan.path.uab.edu). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Messenger RNA sequencing data collection and analysis

Pan-cancer analysis of *KLRB1* was performed using the HPA and TIMER databases. Next, the *KLRB1* expression in tumor tissue and normal or paraoncological tissue was analyzed using samples from the TCGA and GEO databases. Besides, by using the UALCAN database, we obtained the clinical data of EC patients and analyzed the correlation between *KLRB1* expression and these clinical features.

Survival prognosis analysis

The "survminer" package in R studio (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) was used to analyze the data in TCGA to explore the correlation between overall survival (OS) and progression-free survival (PFS) in *KLRB1* and EC patients.

Correlation and gene set enrichment analysis

In order to further explore the relationship between *KLRB1* and EC, we used TCGA data to study the correlation between *KLRB1* and other genes associated with EC. An enrichment analysis of the top 50 genes positively correlated with *KLRB1* was conducted to determine the function of *KLRB1*. A Gene Ontology (GO) enrichment analysis, including biological process (BP), cellular component (CC), and molecular function (MF), was performed using the EnrichGO function in the R package "clusterProfiler". The EnrichKEGG function from the R package clusterProfiler was utilized to conduct Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis.

Immune cell infiltration analysis

Tumor-immune interactions in EC were performed using Cell-type Identification by Estimating Relative Subsets of RNA Transcripts (CIBERSORT). Gene expression profiling data were used to investigate the correlation between *KLRB1* expression on immune cell infiltration and the abundance of tumor-infiltrating immune cells. Finally, *KLRB1* expression levels were investigated in the TIMER database in relation to immune cells infiltration of EC.

Statistical analysis

The abovementioned datasets were generated for all statistical analyses and differences between normal and tumor groups using a *t*-test. Survival curves were generated using the Kaplan-Meier method. A P value less than 0.05 was considered statistically significant.

Results

KLRB1 gene expression in various human cancers

The expression of *KLRB1* in pan-carcer is shown in *Figure 1A*,*1B*. The results showed that the expression of *KLRB1* was low in a majority of cancers, including bladder urothelial carcinoma (BLCA), liver hepatocellular carcinoma (LIHC), thyroid carcinoma (THCA), uterine corpus endometrial carcinoma (UCEC), and others, whereas in the other tumors such as kidney renal clear cell carcinoma (KIRC), *KLRB1* mRNA was highly expressed.

Relationship between KLRB1 expression and patients' status of UCEC

According to our results, the expression level of *KLRB1* was generally low in tumor patients (*Figure 2A*,*2B*). Further sub-group analysis of the UALCAN database showed low *KLRB1* transcription in 546 EC samples. The expression of *KLRB1* were lower in EC patients in subgroup analyses based on cancer stage, ethnicity, race, weight, menopausal status, histological subtypes, and *TP53* mutation status (*Figure 3*).

Survival and prognostic value of KLRB1 in EC

TCGA data were analyzed to further investigate *KLRB1*'s value as a prognostic marker for UCEC. The results shown in *Figure 4A*,*4B* indicated that high expression of *KLRB1* can improve the clinical survival outcome and prolong OS and PFS in patients of EC. Therefore, we suggested that *KLRB1* may be a tumor suppressor gene in EC, contributing to the improvement of patients' survival cycle, and may be a promising prognostic biomarker in EC.

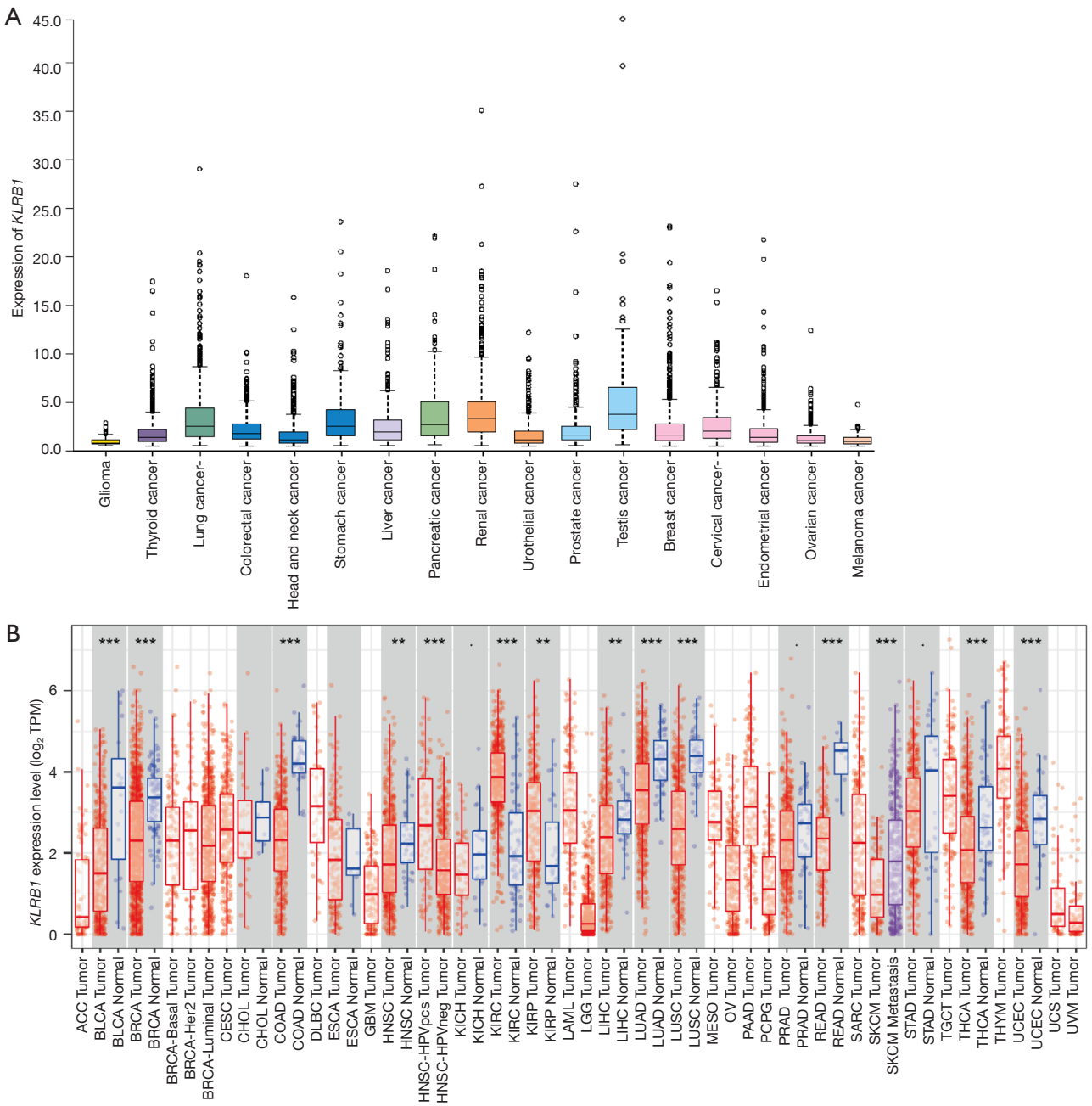

Figure 1 *KLRB1* expression levels in pan-cancer. (A) Expression of *KLRB1* in different tumors in HPA database. These images are available from v21.0.proteinatlas.org. (https://www.proteinatlas.org/ENSG00000111796-KLRB1/pathology). (B) *KLRB1* expression in different types of tumors in the TIMER database (dark spots were automatically generated by the software and is equivalent to splitting characters. It has no practical meaning. For example, DLBC. Tumor represents lymph cancer). **, P<0.01; ***, P<0.001. *KLRB1*, killer cell lectin-like receptor B1; HPA, Human Protein Atlas; TIMER, Tumor IMmune Estimation Resource; DLBC, diffuse large B cell lymphoma; TPM, transcripts per million .

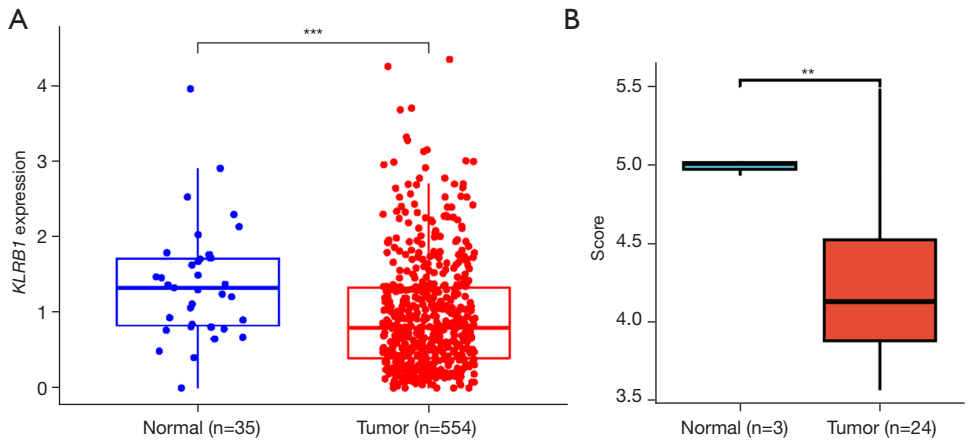

Figure 2 The relative expression of *KLRB1* between normal individuals and EC patients. (A) The relative expression of *KLRB1* in normal and EC samples in TCGA. (B) The relative expression of *KLRB1* in normal and EC samples in GSE115810. **, P<0.01; ***, P<0.001. *KLRB1*, killer cell lectin-like receptor B1; EC, endometrial cancer; TCGA, The Cancer Genome Atlas.

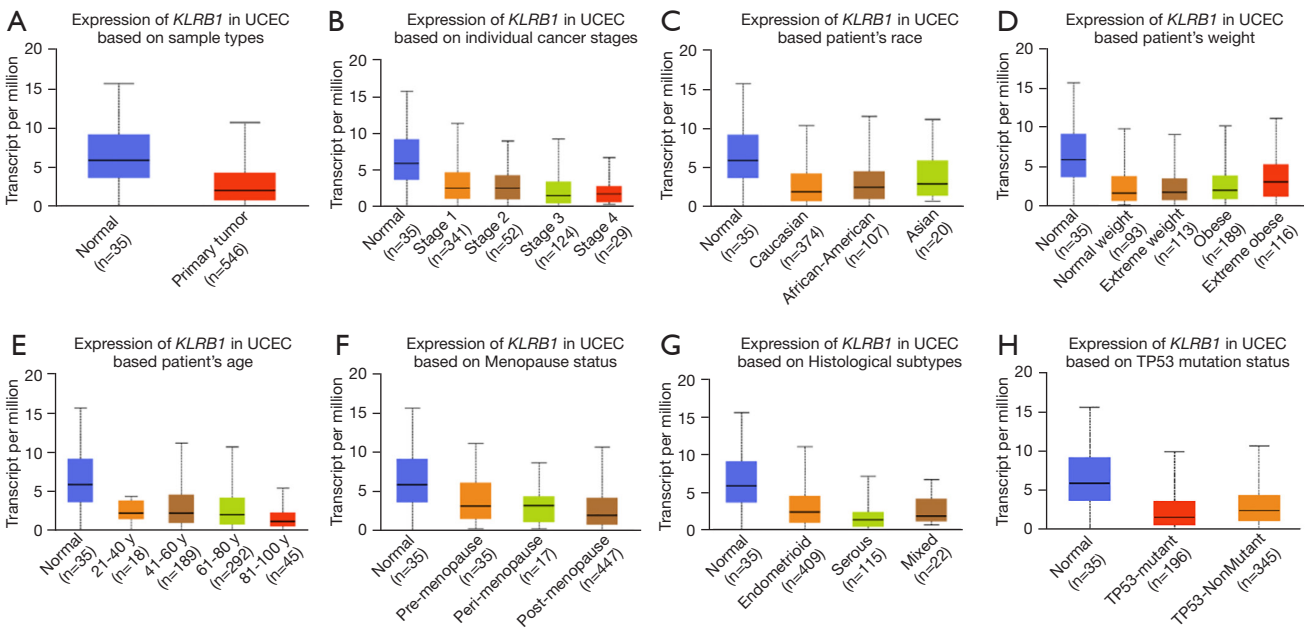

Figure 3 *KLRB1* transcription in subgroups of patients with endometrial cancer, stratified based on cancer stages, patient's age, patient's weight, patient's race, and other criteria (UALCAN) (A-H). *KLRB1*, killer cell lectin-like receptor B1; UALCAN, University of Alabama at Birmingham Cancer data analysis Portal; UCEC, uterine corpus endometrial carcinoma.

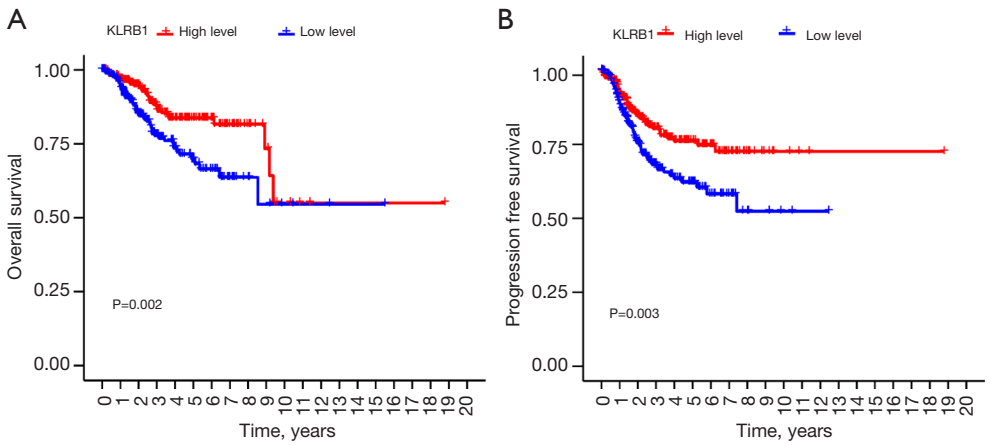

Figure 4 Prognostic value of *KLRB1* mRNA expression in EC patients. (A) Low *KLRB1* expression was associated with poor OS in EC patients in TCGA database. (B) Low *KLRB1* expression was associated with poor PFS in EC patients in TCGA database. *KLRB1*, killer cell lectin-like receptor B1; EC, endometrial cancer; TCGA, The Cancer Genome Atlas; OS, overall survival; PFS, progression-free survival.

Correlation and KLRB1-related gene enrichment analysis

In order to clarify how *KLRB1* works, we searched TCGA for genes associated with *KLRB1* expression for subsequent pathway analysis. Based on the heat map, we identified the top 50 significant gene sets related to *KLRB1* both positively and negatively (*Figure 5A*). By using the "clusterProfiler" R package, we obtained the *KLRB1* positively correlated genes using GO and KEGG enrichment analyses. GO enrichment analysis consisted of three parts: BP, CC, and MF. First, in BP, the results showed that those co-expressed genes were related to immune function, including lymphocyte-mediated immunity and humoral immune response mediated by circulating immunoglobulin. Moreover, the co-expressed genes were found to be enriched in the immunoglobulin complexes, T cell receptor complexes, and the immunoglobulin complexes in the CC. Finally, in MF, the genes were enriched in antigen binding, immunoglobulin receptor binding, immune receptor activity (*Figure 5B*). KEGG enrichment analysis (*Figure 5C*) showed that co-expressed genes were mainly concentrated in cytokine-cytokine receptor interaction, chemokine signaling pathway, NK cell-mediated cytotoxicity, and so on.

Relationship between KLRB1 expression and immune cell infiltration

The above enrichment analysis showed that *KLRB1* was associated with immune response. Therefore, we explored whether *KLRB1* expression was associated with immune cell infiltration. Our study suggested that *KLRB1* had significant correlation with T cells CD8, Tregs, dendritic cells (DC) resting, plasma cells, T cells gamma delta, macrophage M0, eosinophils, and B cells naïve, among others (*Figure 6*). Further research showed that *KLRB1* expression was positively correlated with infiltration levels of T cells CD8 (*Figure 7A*, R=0.35, P=2.4e−07), T cells CD4 memory activated (*Figure 7B*, R=0.31, P=8.5e−06), Tregs (*Figure 7C*, R=0.27, P=0.00012), DC resting (*Figure 7D*, R=0.25, P=0.00028), mast cells resting (*Figure 7E*, R=0.21, P=0.0023), plasma cells (*Figure 7F*, R=0.21, P=0.0033), T cells follicular helper (*Figure 7G*, R=0.2, P=0.0047), and T cells gamma delta (*Figure 7H*, R=0.2, P=0.0052). In contrast, *KLRB1* expression was negatively correlated with that of DC activated (*Figure 7I*, R=−0.36, P=1.3e−07), macrophage M0 (*Figure 7J*, R=−0.36, P=1.9e−07), eosinophils (*Figure 7K*, R=−0.16, P=0.022), B cells memory (*Figure 7L*, R=−0.16, P=0.025), and B cells naive (*Figure 7M*, R=−0.14, P=0.048).

Prognosis analysis of KLRB1 expression with immune infiltration status

Using the TIMER database, we assessed how immune cell infiltration impacts clinical survival outcomes among patients with EC. The results showed that with the greater expressions of myeloid-derived suppressor cells (MDSC), B-cell memory, eosinophils, and T-cell CD4+ in the tumor immune microenvironment, the worse prognosis patients had (*Figure 8A-8D*).

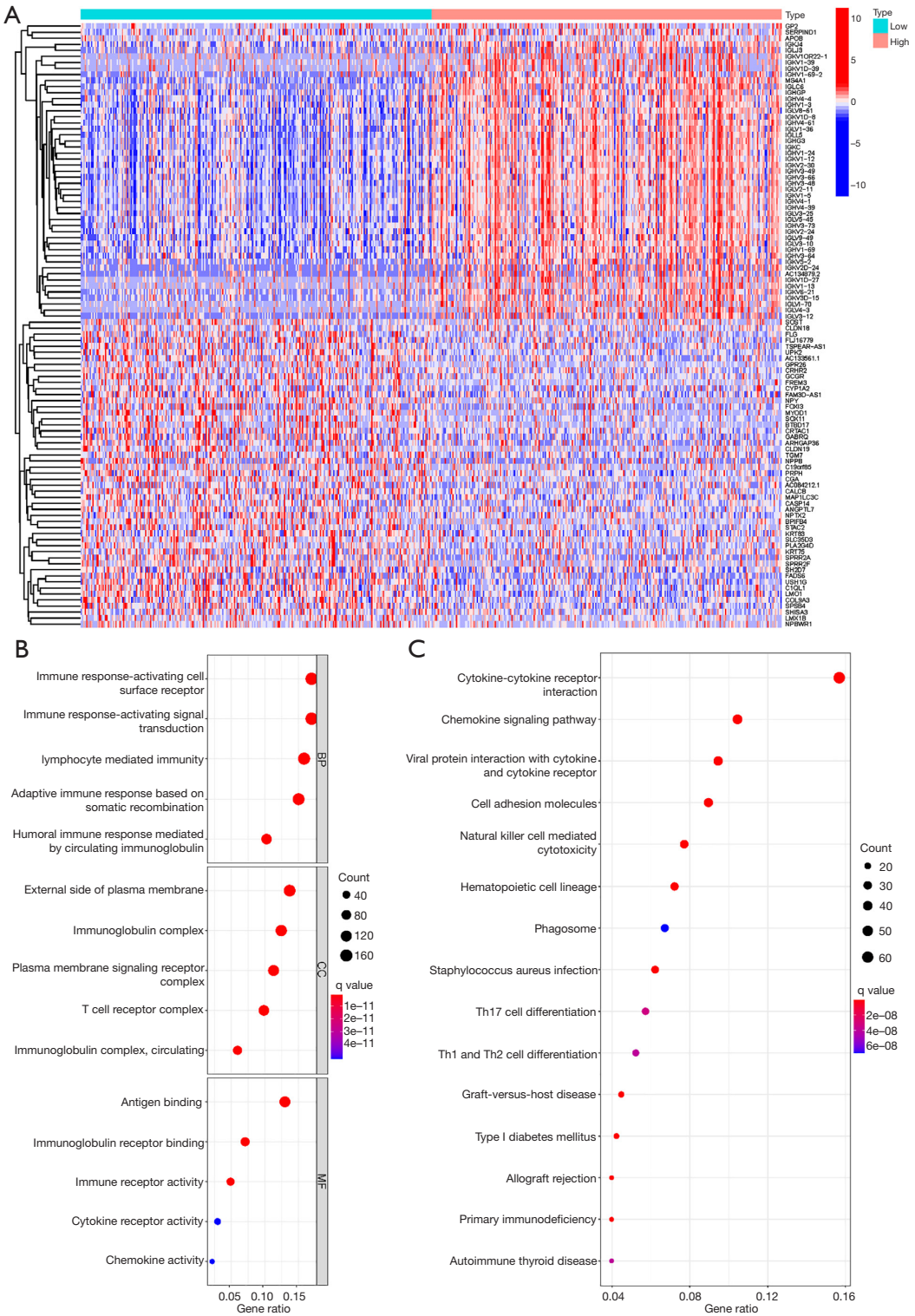

Figure 5 Function and pathway enrichment analysis of *KLRB1* in EC from TCGA. (A) Heat map of differentially expressed genes associated with *KLRB1* in EC. (B) GO annotations of *KLRB1* in EC. (C) Significant KEGG pathway associated with *KLRB1* in EC. *KLRB1*, killer cell lectin-like receptor B1; EC, endometrial cancer; TCGA, The Cancer Genome Atlas; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; CC, cellular component; MF, molecular function.

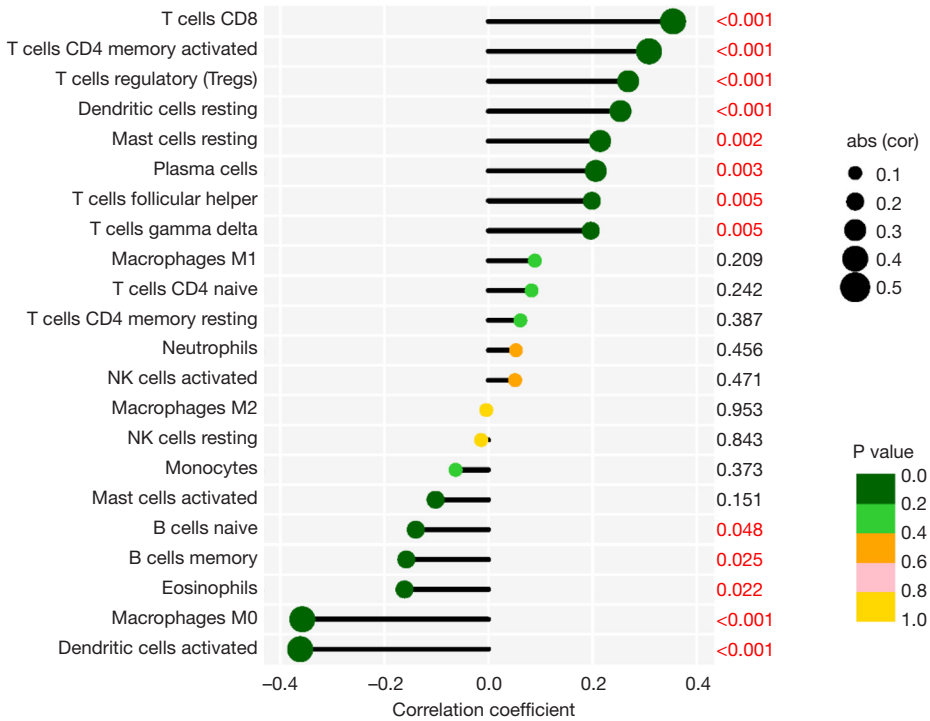

Figure 6 Lollipop chart of *KLRB1* expression level in 22 immune cells. *KLRB1*, killer cell lectin-like receptor B1; NK, natural killer.

Discussion

EC has the characteristics of high mortality and poor prognosis in the advanced stage, which seriously threatens women's health, and the incidence is expected to further increase in the next 10 years (17). There are various treatment options for EC at earlier stages; most of them are curable with surgery and the prognosis is generally good. However, there are limited treatment options for EC at advanced stages (III or IV) and it usually comes with poor prognosis (18). Based on the current situation, how to monitor the progress of EC and predict its survival and prognosis is still a major problem in modern medicine. The 2020 ESGO/ESTRO/ESP guidelines stratify the prognosis of EC patients combining TCGA molecular signature and pathological factors, including lymphovascular space invasion (LVSI) (19). It is well known that clinicopathological factors of EC (such as myometrial invasion, histotype, or lympho space invasion) are a very hot topic. Research from another research group revealed that a high accuracy could be achieved with one-step nucleic acid amplification detection of EC lymph node metastasis (20). A recent study showed that, in EC patients, LVSI has a prognostic value independent of TCGA groups, age, and adjuvant treatment. In particular, the presence of LVSI increased the risk of all-cause mortality, EC death, and recurrent or progressive disease by 1.5–2 times (21). However, how to precisely integrate molecular features with classical pathological factors still needs more basic theoretical and clinical exploration. Therefore, a reliable biomarker is needed to guide us towards more precise diagnosis and treatment. According to the previous studies, *KLRB1* is recognized as a potential prognosis biomarker in breast cancer (22), human esophageal squamous cell carcinoma (14), liver cancer (23), lung adenocarcinoma (24), and bladder cancer (25). The correlation of EC and *KLRB1* expression had not been studied until now. Therefore, our study aimed to investigate the correlation between *KLRB1* and immune cell infiltration in EC and whether it affects the occurrence and development of EC, so as to explore its guiding effect on survival and prognosis of patients with EC.

Recently, studies have suggested that the expression of the gene and protein of *KLRB1* are downregulated to some extent in most tumors (10,26). Tumor immunity is strongly influenced by the *KLRB1* gene and its encoded protein, CD161. A study showed that tumor cell immune escape was associated with the downregulation of CD161

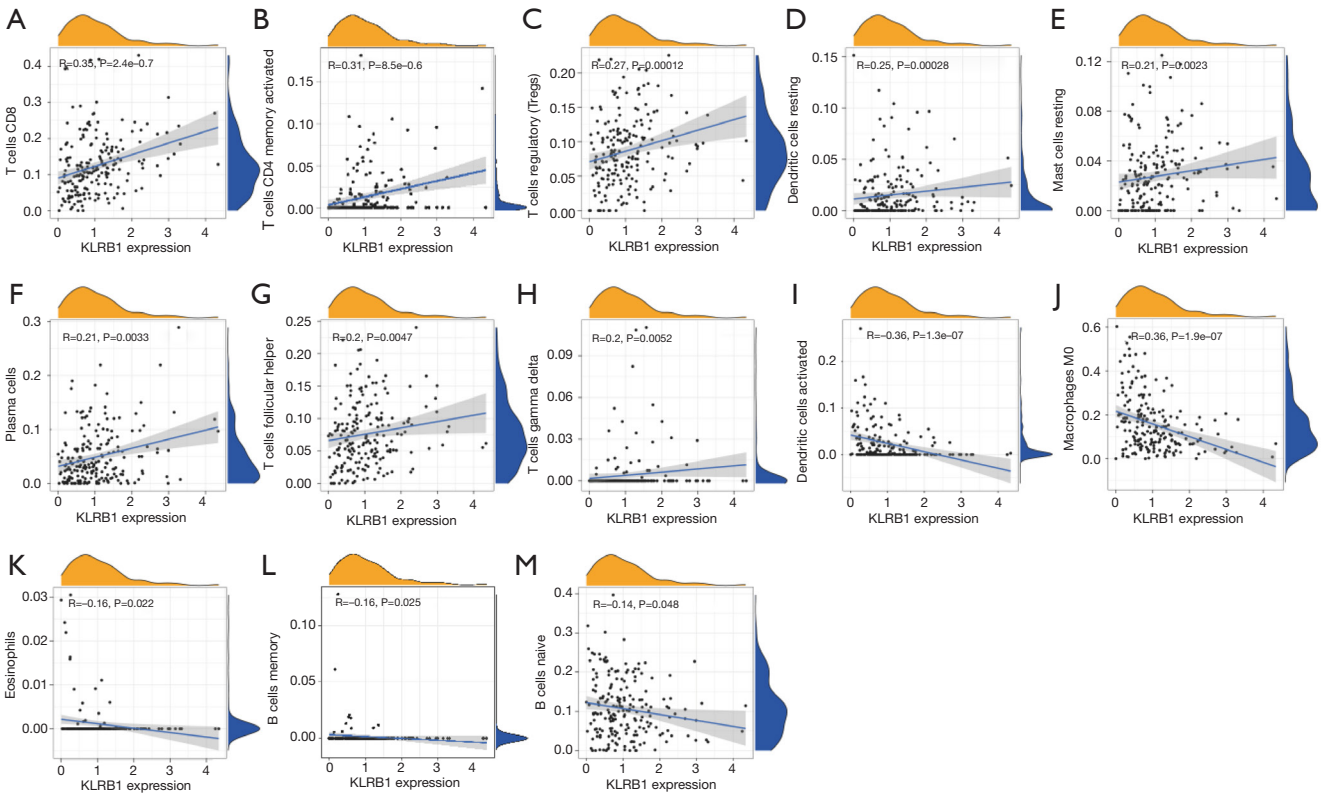

Figure 7 Correlation between *KLRB1* expression and immune cell infiltration. (A-M) T cells CD8, T cells CD4 memory activated, Tregs, DC resting, mast cells resting, plasma cells, T cells follicular helper, T cells gamma delta, DC activated, macrophage M0, eosinophils, B cells memory, and B cells naive. *KLRB1*, killer cell lectin-like receptor B1; DC, dendritic cells.

expression in oropharyngeal squamous cell carcinoma, which may further exacerbate tumor progression (27). If CD161 is highly expressed in T cells, the tumor burden will be significantly reduced, which can improve the survival rate of tumor patients (28). In addition, a relevant study (10) showed that the sensitivity of tumors to chemotherapy drugs has a close relationship with the expression of *KLRB1*. In most tumors, the lower *KLRB1* expression, the better the clinical effect of chemotherapy. These findings suggest that *KLRB1* may serve as a biomarker to help guide clinical drug selection and patient outcomes prognosis. However, the role of CD161 also varies between different tumors. In most tumors, CD161 is associated with a better prognosis, whereas in a small number of cancer types, CD161 has shown a role in promoting adverse tumor outcomes. For example, in glioma, blocking or inactivating CD161 can enhance the killing of gliomas by T cells, which is more conducive to controlling the growth of tumors *in vivo* (24).

In our study, the results indicated that *KLRB1* was downregulated in majority of tumors including EC through pan-cancer analysis which is consistent with previous research (10,26). The correlation of different clinical features with *KLRB1* expression in EC patients was also assessed. The results showed that in the subgroup analysis based on criteria such as patient weight, patient ethnicity, cancer stage, and patient age, the *KLRB1* transcription level of the EC group was significantly increased compared to that of the healthy controls. As compared with all other cancers, the incidence of EC had the strongest association body weight. A previous study showed that 57% of all EC cases are attributable to obesity in America (29). Ethnic differences are also significantly associated with the incidence of EC. A survey study from the United States comparing invasive and non-endometrioid tumors by race showed a significant increase in the prevalence of EC in black women, suggesting that biological racial differences may influence the prevalence of EC (30). Further results showed that patients with higher *KLRB1* expression tended to have better OS than those with low *KLRB1* expression. Above all of these results, *KLRB1* may

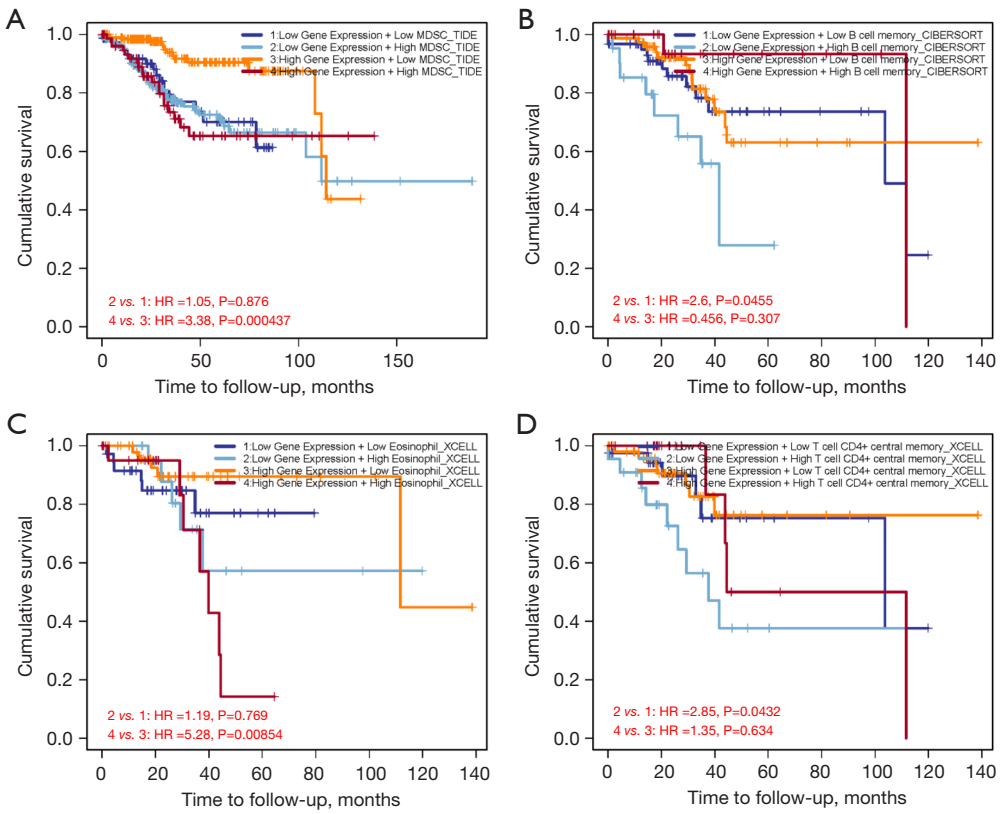

Figure 8 Impact of immune cell infiltration on prognosis in EC patients. (A) Clinical survival outcome of EC patients in the high-myeloid-derived suppressor cells group. (B) Clinical survival outcome of EC patients in the high-B cell memory group. (C) Clinical survival outcome of EC patients in the high-eosinophils group. (D) Clinical survival outcome of EC patients in the high T cell CD4 memory group. EC, endometrial cancer; HR, hazard ratio; CIBERSORT, Cell-type Identification by Estimating Relative Subsets of RNA Transcripts.

influence tumor development in multiple dimensions, and can be used as a biomarker to predict the survival and prognosis of EC patients. Furthermore, the majority cell types in the tumor microenvironment (TME) are immune cells, which can interact with each other to control tumor growth and metastasis, and make great contributions to tumor progression, metastasis, and treatment resistance (31). As a very important checkpoint in the immune microenvironment, CD161 has been shown to cooperate with other immune checkpoints in regulating the TME. These findings might provide great support for the development of new immunotherapy drugs (32). To further explore the correlation between *KLRB1* expression and immune cell infiltration, we conducted the following studies to explore the relationship between *KLRB1* and CD8, Tregs, DC, macrophages, T cells, and so on. Thus, we speculate that the different expression levels of *KLRB1* can change the proportion of some immune cell types in the TME and further affect the occurrence and development of tumors. In summary, our study suggested that the downregulation of *KLRB1* expression in EC was strongly associated with poor survival outcomes, *KLRB1* can be used as a biomarker, and its expression level can predict the tumor development trend and survival prognosis of patients. Unfortunately, the study was conducted only by analyzing information from public databases. Although our research shows that the expression level of *KLRB1* can affect the immune cell types in the TME and can be used as a prognostic marker in EC, the study was only conducted by analyzing information from public databases. How *KLRB1* affects immune cell infiltration in TME and the specific mechanism affecting tumor progression still need to be verified by further clinical

and basic experiments.

Conclusions

We found that the downregulation of *KLRB1* expression in EC was strongly associated with poor survival outcomes. The effect of *KLRB1* on the development and prognosis of EC may be related to its influence on the level of immune cell infiltration in the TME. Our research determined that *KLRB1* can be used as a biomarker, and its expression level can predict the tumor development trend and survival prognosis of patients to a certain extent.

Acknowledgments

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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-23-697/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-697/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-697/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).

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