Original Research

Expression and prognosis analysis of *JMJD5* in human cancers

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1. Abstract

Background: JumonjiC (JmjC) domain-containing protein 5 (*JMJD5*) plays an important part in cancer metabolism. However, the prognostic value of *JMJD5* in most human cancers is unknown yet. We aimed to examine the expression level and prognostic value of *JMJD5*, immune cell infiltration in cancer patients, and simultaneously to examine the correlations among them. **Materials and methods**: The mRNA and protein expression of *JMJD5* were analyzed through online Tumor Immune Estimation Resource (TIMER) or immunohistochemistry (IHC) of tissue microarray sections (TMAs) in cancer versus normal tissues. The Kaplan–Meier Plotter databases were used to assess the prognostic values. The connection between the expression of *JMJD5* and the abundances of six infiltrating immune cells were explored by TIMER in breast cancer (BRCA), liver hepatocellular carcinoma (LIHC), lung squamous cell carcinoma (LUSC), lung adenocarcinoma (LUAD) and stomach adenocarcinoma (STAD). We used the Cox proportional hazards model to investigate the correlations among clinical outcome, the abundance of immune cell infiltration and *JMJD5* expression. **Results**: We found

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that the *JMJD5* expression was obviously lower in BRCA, LIHC and lung cancer (LUC) but higher in STAD than in normal tissues. High expression of *JMJD5* had a better prognosis only in BRCA, LIHC and LUC but a worse prognosis in STAD. The expression of *JMJD5* has a significant connection with the abundance of six kind of infiltrating immune cells. The expression of *JMJD5* plus the number of immune-infiltrating B cells or macrophages may jointly serve as a prognostic marker in the above four cancers. **Conclusion**: We provided novel evidence of *JMJD5* as an essential prognostic biomarker and perspective therapeutic target in BRCA, LUAD, LIHC and STAD.

2. Introduction

Proteins containing JmjC domains have been found as novel demethylase signature motifs contributing to variety of human cancers by means of epigenetic remodeling [1, 2]. It has been predicted that proteins containing the JmjC domain are metalloproteinases folded with copper proteins and candidate enzymes for regulating chromatin remodeling [3]. In addition to histone demethylase activity, some members of the JmjC family, such as *JMJD5* and *JMJD6*, also have protein hydroxylase and RNA hydrogenase activities [4]. In addition to histone modifications, substrates of the JmjC protein family also include many other functional proteins, such as transcription factors, signal molecules and shear-related proteins, all of which are involved in physiological and pathological processes, such as oxidative stress and cell development [5, 6]. Further studies have shown that dysregulation of JmjC family members, e.g., *JMJD5*, *JMJD6*, *JMJD2A* and so on, leads to abnormal growth of embryos or causes tumor cell proliferation and migration.

The protein family which contains JmjC domain has more than 30 members, all of which have the same JmjC domain, which catalyzes the demethylation of mono-, di- or trimethylated lysines [7]. *JMJD5* (also called *KDM8*) is one of the JmjC domain-containing protein family. Y.E. Chin and colleagues reported that *JMJD5* is a cathepsin L-type protease that regulates the hydrolysis and cleavage of histone H3 N-tail protein in the stress situation, resulting in a DNA damage response [8]. *JMJD5* cleaves only Kme1 H3 peptides, with little or even no cleavage function to dimethyl-lysine (Kme2) or trimethyl-lysine (Kme3), indicating that H3 N-tail cleavage plays a role in mediating gene expression [8]. Another study has shown that *JMJD5* may be crucial to cell cycle regulation and that *JMJD5* promotes cyclin A1 expression by affecting histone demethylation (H3K36) at the CDKN1A gene locus, further accelerating the G2/M cell cycle [9]. Knockout of *JMJD5* in mice leads to embryonic lethality, suggesting that *JMJD5* plays a crucial role in mammalian embryogenesis [10].

Studies of a protein similar to *JMJD5* in mice have indicated a potential role for this protein as a tumor suppressor. The interaction of *JMJD5* and *p53* can negatively regulate *p53* function during the processing of cell proliferation and cycle in human lung cancer [11]. *JMJD5* is upregulated under hypoxia and subsequently plays a key part in hypoxia-induced cell proliferation and tumor metabolism in breast cancer cells [12]. Additionally, Hsing-Jien Kung and colleagues reported that *JMJD5* is a suitable therapeutic target for the castration resistance and metabolic adaptation of prostate cancer cells [13]. *JMJD5* is shown as a tumor suppressor function in human liver cancer pathogenesis, and *JMJD5* silencing can promote LIHC cell proliferation through downregulating *CDKN1A* transcription [14]. In contrast, *JMJD5* is instead a lurking oncogene in the development of colon cancer [15].

Based on the abovementioned findings, the expression of *JMJD5* is different in distinct human cancers. However, the detailed expression level, immune cell infiltration and prognostic value of *JMJD5* in most human cancers are still unknown. We sought to examine the expression and prognostic value of *JMJD5* as well as the connection between the expression of *JMJD5* and the infiltration of immune cells in human tumors.

3. Materials and methods

3.1 Data mining of JMJD5 mRNA expression by TIMER database

JMJD5 mRNA expression in various types of tumor tissues was examined by the TIMER [16–18] database (http://timer.cistrome.org/). The differential mRNA expression between tumor and normal tissues for *JMJD5* has been detected using the “Gene-DE” module in TIMER across The Cancer Genome Atlas (TCGA) tumor resources. *JMJD5* mRNA expression was displayed using box plots, showing the median, spread and outliers by RNA-Seq normalized by transcript per million (TPM) across normal and cancerous tissues.

3.2 JMJD5 protein expression analysis by IHC in human TMAs

All these cancer patients’ samples were obtained from Huaihe Hospital of Henan University. The present research has been approved by the Ethics Committee of Huaihe Hospital of Henan University, under the condition of written consent by each patient. All cases were diagnosed histologically by following the World Health Organization classification. All tissues were fixed in 4% buffered formaldehyde and then paraffin embedded to construct TMAs. Eight separate TMAs were generated, containing 14 different types of cancers (Table 1). The detailed IHC protocol has been previously published [19]. The following antibodies were used: rabbit anti-human *JMJD5* polyclonal antibody (1:250, Abcam #28883, USA) and HRP-Polymer anti-Rabbit IHC Kit (Maixin, Fuzhou, China). Stained sections were scanned using a ScanScope

Table 1. All samples used in TMAs.

TCGA Abbr.	Organ	Cancer type	T (no.)	N (no.)
BLCA	Bladder	Urothelial carcinoma	20	20
BRCA	Breast	Invasive ductal carcinoma	20	20
CESC	Cervix	Adenocarcinoma	20	20
		Squamous cell carcinoma	20	20
CHOL	Biliary tract	Cholangiocarcinoma	20	20
COAD	Colon	Adenocarcinoma	20	20
KIRC	Kidney	Renal clear cell carcinoma	20	20
LIHC	Liver	Hepatocellular carcinoma	20	20
LUAD	Lung	Adenocarcinoma	20	20
LUSC		Squamous cell carcinoma	20	20
LULCC		Large cell carcinoma	20	20
OV	Ovary	Serous adenocarcinoma	20	20
PAAD	Pancreas	Invasive ductal carcinoma	20	20
PRAD	Prostate	Adenocarcinoma	20	20
STAD	Stomach	Tubular adenocarcinoma	20	20
UCEC	Uterus	Endometrioid adenocarcinoma	20	20

T2 automated slide scanner (Aperio Technologies, Vista, CA, USA). The IHC staining was independently evaluated by two authors without knowledge of the clinicopathological information. The quantification of IHC was transformed to parameters which give the mean optical density measured using Image-Pro Plus 2.0 (Media Cybernetics, USA), the software determined the final date through optical density cumulative value divided by the target distribution area.

3.3 Survival analysis in Kaplan–Meier Plotter database

The effect of *JMJD5* on relapse-free survival (RFS) in the above significantly expressed cancers were investigated by using Kaplan–Meier plotter [20] (www.kmplot.com). Survival analyses were performed to generate Kaplan-Meier plots. Taking 95% confidence intervals (CIs) as hazard ratios (HRs), we obtained log-rank *p* values.

3.4 Estimation of correlations between JMJD5 expression and the abundances of six tumor-infiltrating immune cells in TIMER

In order to ascertain the correlations between *JMJD5* expression and six tumor-infiltrating immune cells (B cells, $CD4^+$ T cells, $CD8^+$ T cells, macrophages, neutrophils and myeloid dendritic cells) in BRCA, LIHC, LUAD, LUSC and STAD, we chose to use the TIMER database. The TIMER database is a web resource which is quite smart in terms of systematic evaluations of the clinical outcomes of different immune cells in various types of cancers. The "Immune" module in TIMER was used to find the relation between genomic changes and immune infiltrates in TCGA. At the first step, we selected the "Gene" module and entered in *JMJD5* for gene expression, and secondly, enter immune infiltrating cell (B cells, $CD4^+$ T cells, $CD8^+$ T cells, macrophages, neutrophils and myeloid dendritic cells) separately, then a heatmap with numbers was generated to show the Spearman's Rho through various cancer types adjusted by tumor purity. Once the interested cell on the heatmap was selected, a scatter plot was created to show the relationship between the *JMJD5* expression and infiltrate estimation value. Furthermore, we selected the tumor "Purity" to adjust our analysis as most immune cell types have negative correlation with tumor purity. Partial Spearman's association analysis was used to determine the correlation coefficient.

3.5 Prognostic impact of JMJD5 expression combined with tumor-infiltrating immune cells

Patients with BRCA, LIHC, LUAD, LUSC and STAD were divided into four groups as follows: (1) low *JMJD5* expression + low tumor-infiltrating immune cells; (2) low *JMJD5* expression + high tumor-infiltrating immune cells; (3) high *JMJD5* expression + low tumor-infiltrating immune cells; and (4) high *JMJD5* expression + high tumor-infiltrating immune cells. A Cox proportional hazards model was used to draw Kaplan–Meier plots for *JMJD5* expression and immune infiltrates to visualize the survival differences. The expression of *JMJD5* and six immune infiltrates was divided into low and high levels by 50%. *p* values of the log-rank test for comparing survival curves of four groups (2 vs. 1 and 4 vs. 3) are shown in each plot.

3.6 Statistical analysis

The data were analyzed with GraphPad Prism 5 and presented as the means ± SD. Statistical significance was calculated with a *t*-test. The correlation of *JMJD*5 expression and immune infiltrates was calculated through partial Spearman's correlation analysis. $p < 0.05$ was treated as statistically significant.

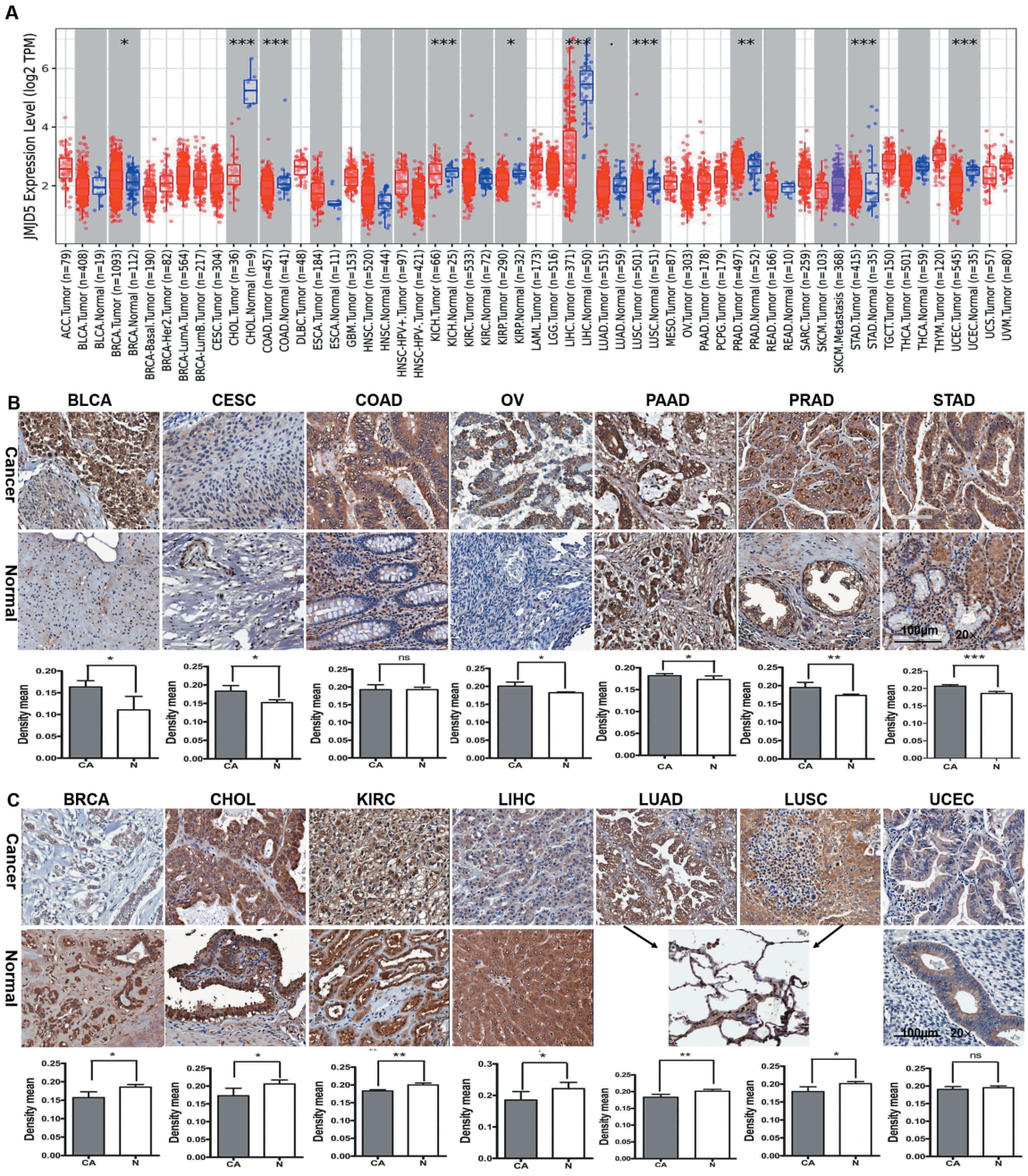

Fig. 1. Human mRNA and protein expression of *JMJD5* in various tumor tissues compared to normal tissues. (A) Box plots showing the distributions (median, spread and outliers) of the *JMJD5* mRNA levels (log2 TPM) by RNA-seq data as displayed in gray columns when normal data were available. The number of samples is shown at the bottom. p value significance is indicated as follows: $0 \leq$ *** $< 0.001 \leq$ ** $< 0.01 \leq$ * $< 0.05 \leq \cdot < 0.1$. (B) The protein expression of *JMJD5* was significantly higher in BLCA, CESC, OV, PAAD, PRAD and STAD than in the respective normal tissues. (C) *JMJD5* protein expression was significantly lower in GHOL, KIRC, LIHC, LUAD and LUSC compared to the respective normal tissues. The quantification of IHC results was transformed to the mean optical density measured by Image-Pro Plus 2.0. Bars show the means $\pm$ SD. Statistical differences were noted as *$p < 0.05$, **$p < 0.001$ and ***$p < 0.0001$. Original magnification: 20×. Scale bar: 100 μm.

4. Results

4.1 Expression of JMJD5 varies in distinct human cancers

We investigated the *JMJD5* mRNA expression in various cancers using TIMER. Our results presented that the *JMJD5* mRNA expression was significantly higher in PRAD (**) and STAD (***) but lower in BRCA (*), CHOL (***), colon adenocarcinoma (COAD) (***), kidney renal clear cell carcinoma (KIRC) (*), LIHC (***), LUAD (·), LUSC (***) and uterine corpus endometrial carcinoma (UCEC) (***) by comparing each tissue with its normal one (Fig. 1A).

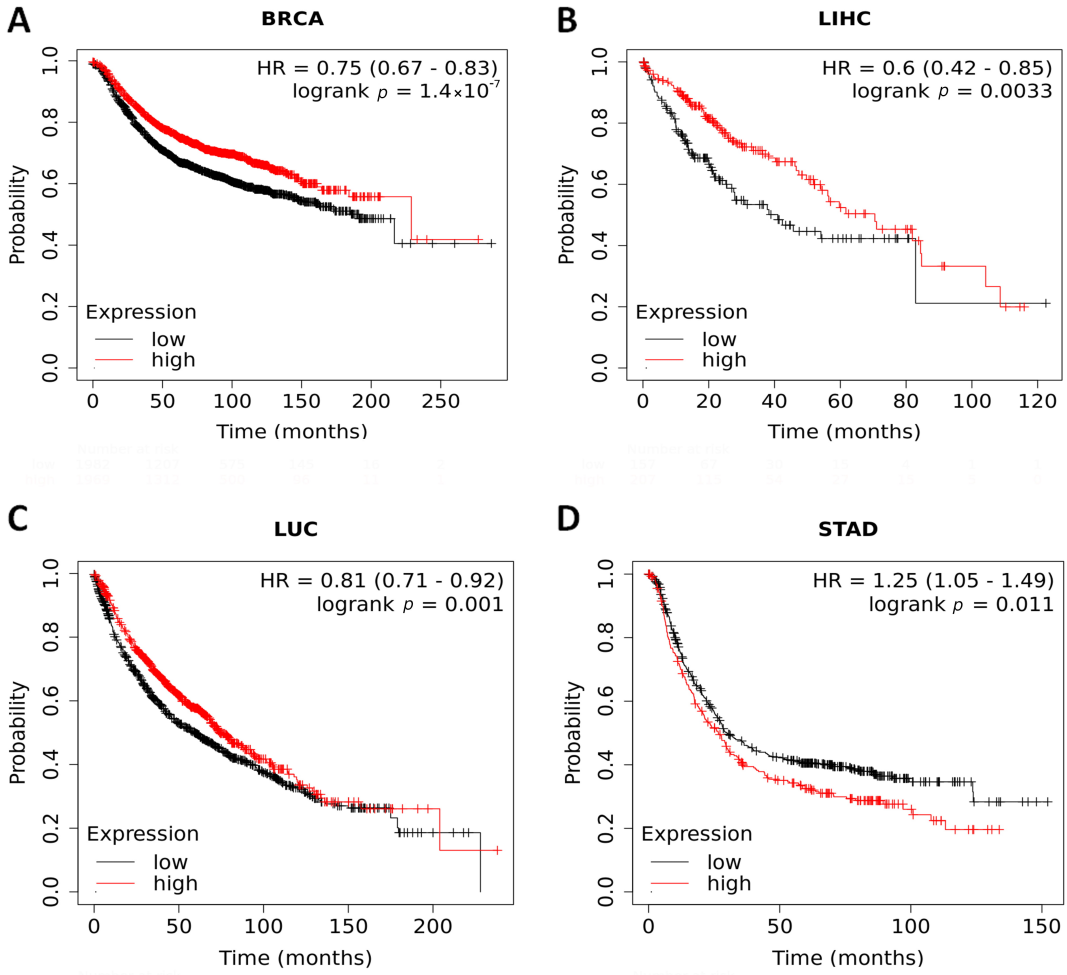

Fig. 2. Kaplan–Meier survival curves comparing the low and high expression of *JMJD5* in BRCA, LIHC, LUC and STAD patients. (A) RFS of BRCA. (B) RFS of LIHC. (C) RFS of LUC. (D) RFS of STAD. The red curve indicates patients with high *JMJD5* expression, while the black curve indicates patients with low *JMJD5* expression. $p < 0.05$ was supposed to have statistical difference.

To confirm *JMJD5* protein expression and estimate its clinical significance in cancers, we investigated the *JMJD5* protein expression in TMAs using IHC. It is now clear the *JMJD5* protein expression was significantly higher in bladder urothelial carcinoma (BLCA) (*), cervical squamous cell carcinoma (CESC) (*), ovarian cancer (OV) (*), pancreatic invasive ductal carcinoma (PAAD) (*), PRAD (**) and STAD (***) compared to the respective normal tissues (Fig. 1B) but was significantly lower in BRCA (*), CHOL (*), KIRC (**), LIHC (*), LUAD (**) and LUSC (*) compared to the respective normal tissues (Fig. 1C). The *JMJD5* protein level was higher in COAD than in the respective normal tissue, but there was no statistically significant difference (Fig. 1B). The *JMJD5* protein level was lower in UCEC compared to the respective normal tissue, but there was no statistically significant difference (Fig. 1C). IHC staining showed that *JMJD5* was localized in different parts of tumor cells, including nuclei, cytoplasm or both, as follows: only in nuclei in BRCA and LUAD (Fig. 1C); only in cytoplasm in COAD, OV, PAAD, PRAD, STAD, CHOL, KIRC, LIHC, LUSC and UCEC (Fig. 1B,C); and in both nuclei and cytoplasm in BLCA and CESC (Fig. 1B). Additionally, we found that the protein expression and localization of *JMJD5* varied according to the different pathological types of tumors. For example, the protein level of *JMJD5* was lower in LUC (LUAD, LUSC and large cell carcinoma (LULCC)) compared to the normal tissues; however, there was an obvious difference in LUAD (**) and LUSC (*) (Fig. 1C) but no obvious difference in LULCC (data not shown). *JMJD5* protein expression was observed only in nuclei in LUAD (Fig. 1C), only in the cytoplasm in LUSC (Fig. 1C) and in both nuclei and cytoplasm in LULCC (data not shown).

4.2 Expression of JMJD5 serves as a prognostic marker in BRCA, LIHC, LUC and STAD

We next determined whether the *JMJD5* expression has any effect on the prognosis of cancer patients. Among the cancers (BLCA, BRCA, CESC, OV, PAAD, PRAD, STAD, CHOL, KIRC, LIHC, LUAD and LUSC)

with significantly different expression of *JMJD5*, we identified *JMJD5* as a prognostic marker in BRCA (n = 3955, RFS: HR = 0.75, 95% CI from 0.67 to 0.83, log-rank $p = 1.4 \times 10^{-7}$) (Fig. 2A), LIHC (n = 364, RFS: HR = 0.6, 95% CI from 0.42 to 0.85, log-rank $p = 0.0033$) (Fig. 2B), LUC (n = 1927, RFS: HR = 0.81, 95% CI from 0.71 to 0.92, log-rank $p = 0.001$) (Fig. 2C) and STAD (n = 881, RFS: HR = 1.25, 95% CI from 1.05 to 1.49, log-rank $p = 0.011$) (Fig. 2D). However, the expression of *JMJD5* had no correlation with the survival rate in other types of cancer (BLCA, CESC, CHOL, KIRC OV, PAAD and PRAD) (**Supplementary Fig. 1**), except for the above four types of cancer (BRCA, LIHC, LUC and STAD). These results indicated that BRCA, LIHC and LUC patients with significantly higher expression of *JMJD5* had an improved survival rate. In contrast, STAD patients with low *JMJD5* expression were associated with a better survival rate. Thus, the expression of *JMJD5* impacts RFS and may serve as a prognostic marker in BRCA, LIHC, LUC and STAD.

4.3 Expression of JMJD5 is strongly correlated with tumor-infiltrating immune cells in BRCA, LIHC, LUAD, LUSC and STAD

We focused on and analyzed the correlation between *JMJD5* expression and the quantity of six infiltrating-immune cells (B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, macrophages and myeloid dendritic cells) in BRCA, LIHC, LUAD, LUSC and STAD. Our results demonstrated that in BRCA, *JMJD5* expression significantly negatively correlated with tumor purity and neutrophil infiltration and positively correlated with the infiltration of B cells, $CD8^+$ T cells and macrophages but has no relationship with $CD4^+$ T cells and myeloid dendritic cells (Fig. 3A). The *JMJD5* expression in LIHC had no relationship with tumor purity or infiltration of $CD4^+$ T cells, macrophages, neutrophils and myeloid dendritic cells, but it was significantly negatively correlated with infiltrated B cells and significantly positively correlated with $CD8^+$ T cells (Fig. 3B). In LUAD, the expression of *JMJD5* significantly negatively correlated with tumor purity, and positively correlated with the infiltration of B cells, $CD4^+$ T cells and myeloid dendritic cells but had no relationship with $CD8^+$ T cells, macrophages or neutrophils (Fig. 3C). The *JMJD5* expression in LUSC significantly negatively correlated with tumor purity and positively correlated with the infiltration of B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils and myeloid dendritic cells, but had no relationship with macrophages (Fig. 3D). The *JMJD5* expression in STAD had no relation with tumor purity but was significantly positively correlated with the infiltration of B cells, $CD4^+$ T cells, $CD8^+$ T cells, macrophages, neutrophils and myeloid dendritic cells (Fig. 3E). In conclusion, these results suggested that the *JMJD5* expression strongly correlates with immune cell infiltration in BRCA, LIHC, LUAD, LUSC and STAD.

4.4 The combination of JMJD5 expression with either B cell tumor infiltration or macrophage tumor infiltration may serve as a new tumor prognostic marker

The Kaplan–Meier plots showed that the survival rate of low *JMJD5* expression patients with higher B cell tumor infiltration were much better than those with lower B cell tumor infiltration in BRCA (n = 1100, OS: HR = 0.658, $p = 0.0487$) (Fig. 4A; 2 vs. 1) and LUAD (n = 515, OS: HR = 0.67, $p = 0.039$) (Fig. 4B; 2 vs. 1). The survival rate of high *JMJD5* patients with lower macrophage tumor infiltration were much better than those with higher macrophage infiltration in LIHC (n = 371, OS: HR = 1.72, $p = 0.0158$) (Fig. 4C; 4 vs. 3). The survival rate of low *JMJD5* expression patients with lower macrophage infiltration is much better than those with higher macrophage infiltration in STAD (n = 415, OS: HR = 2.26, $p = 0.00035$) (Fig. 4D; 2 vs. 1). In summary, the combination of *JMJD5* expression with either B cell tumor infiltration or macrophage tumor infiltration may serve as a new tumor prognostic marker.

5. Discussion

The JmjC domain-containing protein family contains more than 30 members, and many members are aberrantly expressed or dysregulated in many kinds of human cancers and regulate the proliferation and invasion of tumor cells [21, 22]. For example, the aberrant expression of some family members, such as *PHF8*, *KDM3B* and *JMJD2A*, promotes the proliferation and metastasis of tumor cells in PRAD and BRCA [6, 23]. *JMJD5* belongs to the JmjC domain-containing protein family, but the expression level, prognostic value and the correlation of tumor immune infiltration in most human cancers are still unclear. From our study, we reported the protein expression of *JMJD5* in almost all human cancers for the first time, and we found that *JMJD5* was overexpressed in STAD and that high expression of *JMJD5* indicated poor survival. In contrast, low expression levels of *JMJD5* were found in BRCA, LIHC and LUC, and low *JMJD5* expression was yielded a poor outcome. Therefore, *JMJD5* is not only a potential prognostic biomarker but may also be a therapeutic target for BRCA, LIHC, LUC and STAD.

JMJD5 is a nuclear protein which mostly move between cell nucleus and cytoplasm [4, 24]. *JMJD5* has many enzyme activities, including H3K36me2 demethylation activity, C3 arginine hydroxylation activity, endo-/exopeptidase activity at arginine-methylated histones and endopeptidase activity at lysine-methylated histones, and this function may closely correlate with various human diseases, such as tumors, diabetes and so on, through epigenetic regulation. *JMJD5* is involved in different physiological and pathological processes. Recent molecular mechanism study showed that *JMJD5* activates or suppresses gene expression at the transcriptional and posttranslational lev-

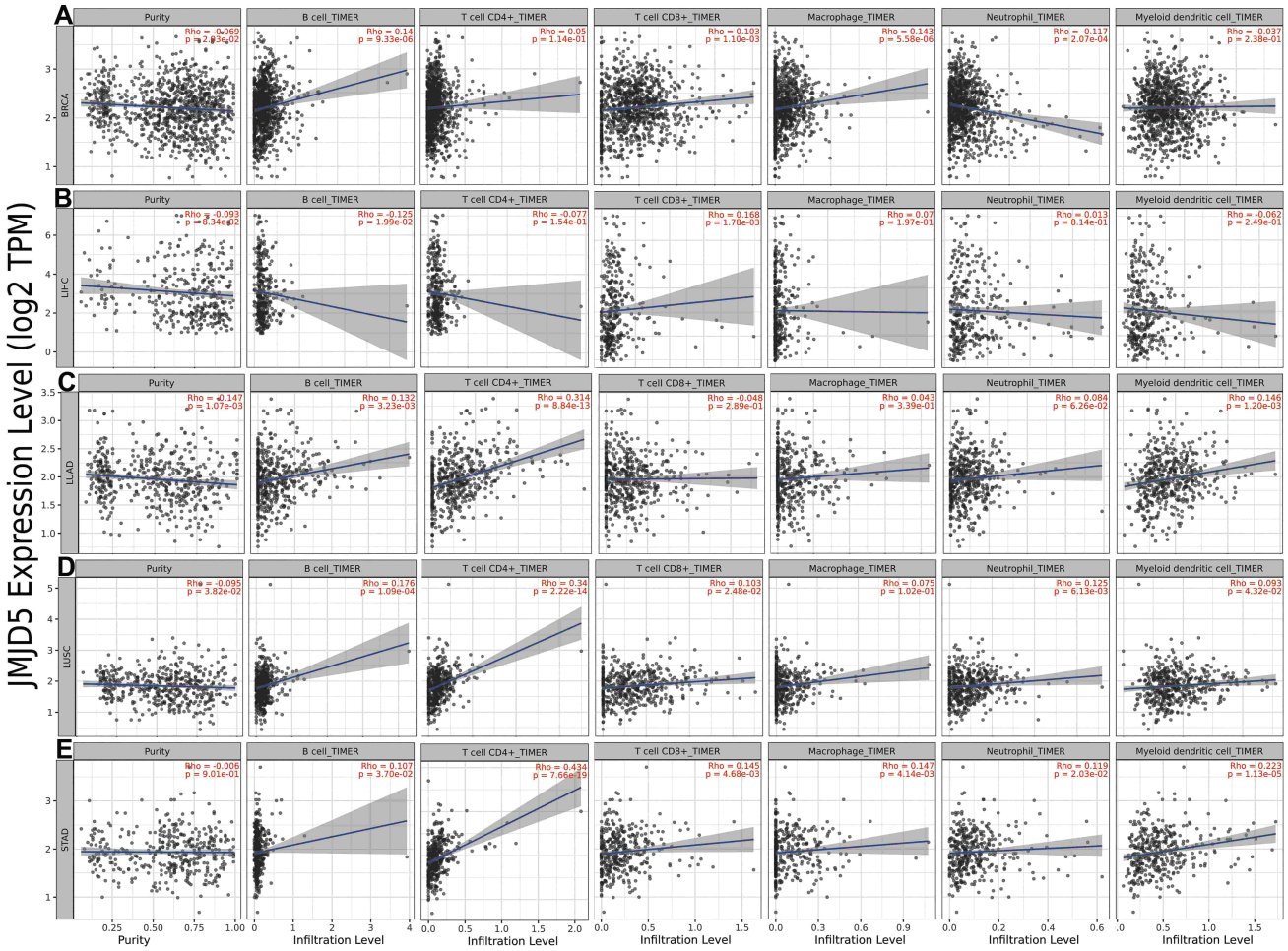

Fig. 3. Correlation of *JMJD5* expression with six tumor-infiltrating immune cells in BRCA, LIHC, LUAD, LUSC and STAD. (A) In BRCA, *JMJD5* expression significantly negatively correlated with tumor purity and neutrophil infiltration and positively correlated with the infiltration of B cells, $CD8^+$ T cells and macrophages but has no relationship with $CD4^+$ T cells and myeloid dendritic cells. (B) In LIHC, the *JMJD5* expression had no relationship with tumor purity or infiltration of $CD4^+$ T cells, macrophages, neutrophils and myeloid dendritic cells, but it had a significant negative correlation with infiltrated B cells and significant positive correlation with $CD8^+$ T cells. **(**C**)** In LUAD, the *JMJD5* expression had a significant negative correlation with tumor purity and a positive correlation with the infiltration of B cells, $CD4^+$ T cells and myeloid dendritic cells as well as no relation with $CD8^+$ T cells, macrophages or neutrophils. (D) In LUSC, the *JMJD5* expression significantly negatively correlated with tumor purity and positively correlated with the infiltration of B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils and myeloid dendritic cells as well as no relation with macrophages (E) In STAD, the expression of *JMJD5* had no relationship with tumor purity but a significantly positively correlated with the tumor-infiltrating B cells, $CD4^+$ T cells, $CD8^+$ T cells, macrophages, neutrophils and myeloid dendritic cells. $p < 0.05$ was considered as significant.

els. Thus, *JMJD5* may play a role in pro-cancer or anti-cancer activity depending on context.

Recent research has reported that immune cells present in the microenvironment of tumor either inhibit or support the growth and development of tumors [25]. Tumor-infiltrating immune cells contain those mediating adaptive immunity, T lymphocytes, dendritic cells and occasional B cells as well as effectors of innate immunity, macrophages, polymorph nuclear leukocytes and rare natural killer cells [26]. Recently, studies have shown that the B cells existing in human tumors is associated with a promising response to immunotherapy [27–29]. Furthermore, macrophages existing in tumors named tumor-associated macrophages are reprogrammed to suppress lymphocyte functions by releasing of inhibitory cytokines [30, 31]. To date, JmjC domain-containing protein family has been hardly reported in terms of in-depth study in immuno-oncology. There is no report on the relationship between *JMJD5* and immune cell infiltration. Our results revealed that the mRNA expression of *JMJD5* may reflect immune cell infiltration in BRCA, LIHC, LUAD, LUSC and STAD and that infiltration by high B cells is a key discriminative feature of patients with low *JMJD5* in BRCA and LUAD with improved survival. Additionally, we found that the number of immune-infiltrating macrophages combined with *JMJD5* expression may serve as a prognostic marker for LIHC and STAD. This finding may have broad applications in tumor targeting therapy and immunotherapy.

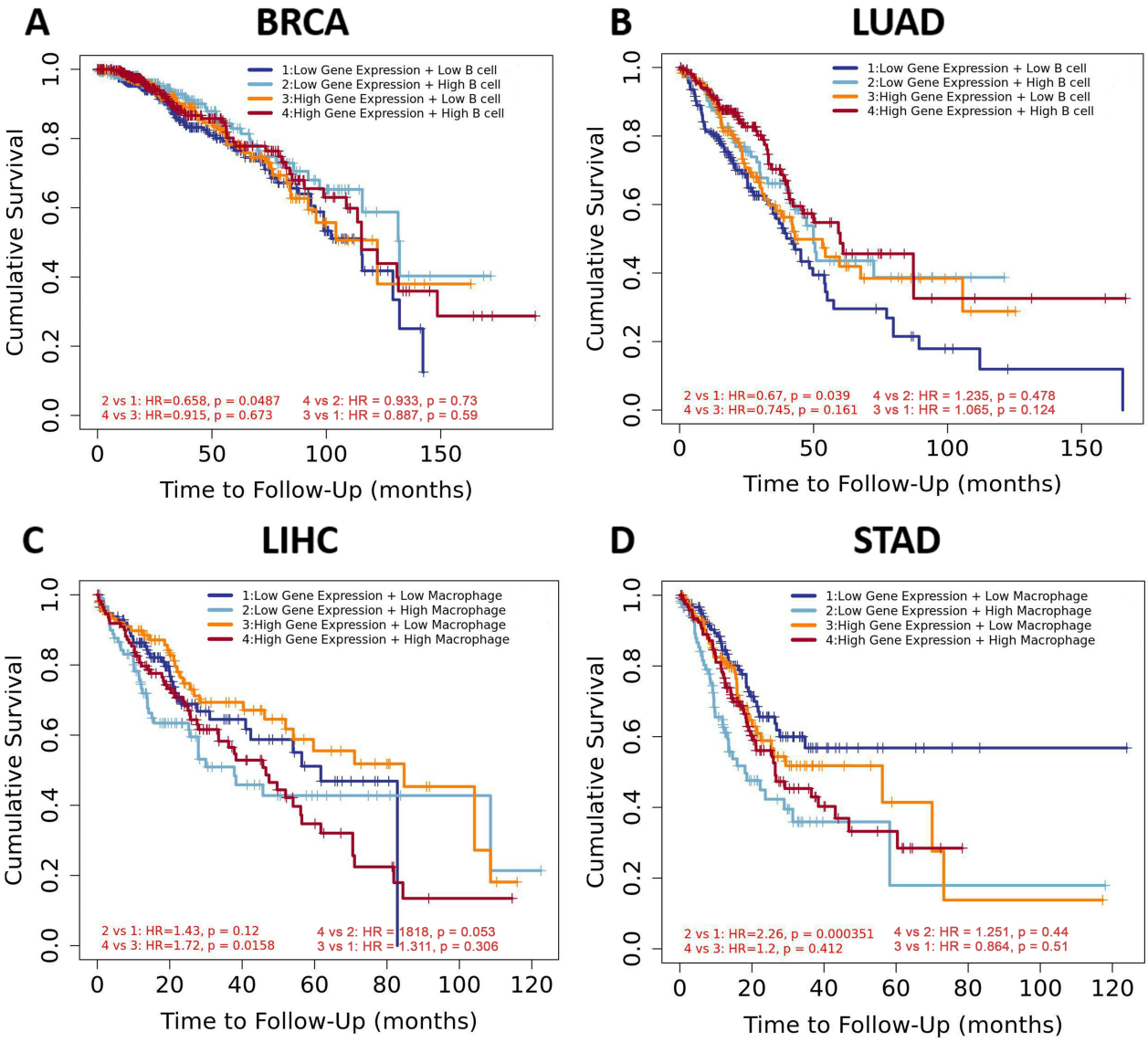

Fig. 4. Kaplan–Meier plots for expression level and immune cell infiltrates to visualize the survival differences in BRCA, LUAD, LIHC and STAD. (A and B) The survival rate of low *JMJD5* expression patients with higher B cell tumor infiltration were much better than those with lower B cell tumor infiltration in BRCA (A) and LUAD (B). (C) LIHC patients with high expression of *JMJD5* had an improved survival rate with lower macrophage tumor infiltration compared to those with higher macrophage tumor infiltration. (D) The survival rate of low *JMJD5* expression patients with lower macrophage infiltration is much better than those with higher macrophage infiltration in STAD.

6. Conclusions

In summary, we provided novel evidence of *JMJD5* as an essential prognostic biomarker in BRCA, LIHC, LUAD and STAD. Our future studies will aim to determine how to regulate the expression of *JMJD5* and tumor-infiltrating B cells or macrophages in BRCA, LUAD, LIHC and STAD, which may be a promising therapeutic approach in tumor treatment.

7. Author contributions

ZS designed the study; HL, QL, HJ, JZ, HZ and XM performed the research; ZS, HL and QL analyzed the data and wrote the paper; WS, HL and QL revised the paper; LW and RD contributed reagents and materials. All authors reviewed and approved the final manuscript.

8. Ethics approval and consent to participate

All samples were obtained from patients with cancers who had surgery in Huaihe Hospital of Henan University, and written informed consent was obtained from

each patient. This study was approved by ethics committee of Huaihe Hospital of Henan University, code: HUMOR2020-112.

9. Acknowledgment

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10. Funding

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11. Conflict of interest

The authors declare no conflict of interest.

12. References

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Supplementary material: Supplementary material associated with this article can be found, in the online version, at https://www.fbscience.com/Landmark/articles/10.52586/4981.

Abbreviations: BLCA, Bladder urothelial carcinoma; BRCA, Breast invasive carcinoma; CESC, Cervix squamous cell carcinoma; CHOL, Cholangiocarcinoma; COAD, Colon adenocarcinoma; HR, Hazard ratio; IHC, Immunohistochemistry; JmjC, JumonjiC; *JMJD5*, JumonjiC domain-containing protein 5; KIRC, Kidney renal clear cell carcinoma; LIHC, Liver hepatocellular carcinoma; LUC, Lung cancer; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; OS, Overall survival; OV, Ovarian cancer; PAAD, Pancreas invasive ductal carcinoma; PRAD, Prostate adenocarcinoma; RFS, Relapse-free survival; STAD, Stomach adenocarcinoma; TCGA, The Cancer Genome Atlas; TMA, Tissue microarray; 95% CIs, 95% confidence intervals; UCEC, Uterine corpus endometrial carcinoma.

Keywords: Cancers; *JMJD5*; Expression; Immune cell infiltration; Prognosis; Biomarker

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