Cancer-testis antigen KK-LC-1 is a potential biomarker associated with immune cell infiltration in lung adenocarcinoma

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Abstract

Background: Cancer-testis antigens (CTAs) have emerged as potential clinical biomarkers targeting immunotherapy. KK-LC-1 is a member of CTAs, which has been demonstrated in a variety of tumors tissues and been found to elicit immune responses in cancer patients. However, the expression level and immune infiltration role of KK-LC-1 in lung adenocarcinoma (LUAD) remains to be elucidated.

Methods: In this study, the mRNA expression and overall survival rate of KK-LC-1 were evaluated by the TIMER and TCGA database in LUAD tissues and KK-LC-1 expression was further validated by clinical serum samples using quantitative RT-PCR. The relationship of KK-LC-1 with clinicopathologic parameters was analyzed. ROC curve result showed that miR-1825 was able to distinguish preoperative breast cancer patients from healthy people and postoperative patients. Then, the ROC curves were used to examine the ability of KK-LC-1 to distinguish preoperative LUAD patients from healthy and postoperative patients. The correlation between KK-LC-1 and infiltrating immune cells and immune marker sets was investigated via TIMER, TISIDB database, and CIBERSORT algorithm. The Kaplan-Meier plotter was used to further evaluate the prognostic value based on the expression levels of KK-LC-1 in related immune cells.

Results: The results showed that KK-LC-1 was significantly over-expressed in LUAD, and high levels of expression of KK-LC-1 were also closely correlated with poor overall survival. We also found that KK-LC-1 associated with TMN stage, NSE and CEA. The ROC curve result showed that KK-LC-1 was able to distinguish preoperative LUAD cancer patients from healthy people and postoperative patients. Moreover, KK-LC-1 had a larger AUC with higher diagnostic sensitivity and specificity than CEA. Based on the TIMER, TISIDB database, and CIBERSORT algorithm, the expression of KK-LC-1 was negatively correlated with CD4+ T cell, Macrophage, and Dendritic Cell in LUAD. Moreover, Based on the TIMER database, KK-LC-1 expression had a remarkable correlation with the type markers of Monocyte, TAM, M1 Macrophage, and M2 Macrophage. Furthermore, KK-LC-1 expression influenced the prognosis of LUAD patients by directly affecting immune cell infiltration by the Kaplan-Meier plotter analysis.
Introduction
Lung cancer, the most common and fatal cancer in the world, causes more than 2.20 million new cases and 1.79 million patients die per year [1, 2]. Among all histological types, non-small cell lung cancer (NSCLC) makes up 80–85% of all lung cancer cases. Lung adenocarcinoma (LUAD) is the main member of NSCLC, which is the most invasive one [3]. Despite the conventional radiotherapy, chemotherapy and surgery have taken a leap forward, the five-year survival rate of NSCLC is still poor [4]. Recently, immunotherapy has emerged as an alternative treatment for lung cancer. For instance, pembrolizumab, an inhibitor of programmed death-1 (PD-1), has already been applied in the clinic [5]. However, the clinical results were still unsatisfactory because of drug resistance and adverse reactions [4]. Therefore, it is urgent to explore a reliable prognostic biomarker that can predict the prognosis of LUAD and improve the immunotherapy of patients.

Cancer-testis antigens (CTAs) may be suitable targets for cancer immunotherapy due to their immune-privileged properties. CTAs expressed restrictively in normal tissue except for testicular germ cells and various tumour types, including epithelial ovarian cancer, lung cancer, and cervical carcinoma [6–8]. Many reports found that CTAs were remarkably correlated with the oncogenesis, metastasis, and unfavorable prognosis of tumors [9]. CTAs have strong immunogenicity and induce humoral immunity in several types of cancers [10, 11]. Kita-kyushu lung cancer antigen 1 (KK-LC-1), called CT83 or CXORF61, is a CTA that has epitope peptides recognised by cytotoxic T lymphocytes (CTLs) [12]. Fukuyama et al. first reported it in LUAD in 2006, which consisted of 556 base pair and located in chromosome Xq22 [12]. In recent years, the researches of KK-LC-1 mainly focused on the change of expression in different cancer tissues, especially gastric cancer, and the different therapeutic strategies such as photodynamic therapy and vaccine [13–17]. However, the expression level of KK-LC-1 in LUAD serum samples and the relationship between the expression level of KK-LC-1 with immune infiltration remain to be elucidated.

In this study, we analyzed the KK-LC-1 expression by using The Cancer Genome Atlas (TCGA) database. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to further confirm KK-LC-1 expression in LUAD serum samples. Then, we explored the prognostic value of KK-LC-1 by plotting the survival curve and using the Kaplan-Meier plotter. In addition, we estimated the association between KK-LC-1 expression and tumor-infiltrating immune cells by using the Tumor Immune Estimation Resource (TIMER), CIBERSORT, and TISIDB database. Our results indicated that KK-LC-1 plays a non-redundant role in LUAD and is related to immune response.
The relative expression levels of KK-LC-1 was calculated by $2^{-\Delta\Delta CT}$ method.

**TIMER database**

TIMER database ([https://cistrome.shinyapps.io/timer/](https://cistrome.shinyapps.io/timer/)) is a comprehensive online tool, which can not only systematically evaluate immune infiltrates of different cancers, but also compare the differential expression between cancer and normal tissue [18]. In present study, we used the TIMER database to explore the difference KK-LC-1 expression between various cancers and adjacent normal samples. Then, we analyzed the relationship between KK-LC-1 and immune cell infiltration in LUAD. Moreover, the relationship between immune cell infiltration and corresponding gene markers was analyzed.

**TCGA database**

The gene expression profiles were downloaded from the TCGA database ([http://portal.gdc.cancer.gov/](http://portal.gdc.cancer.gov/)). We analyzed the expression of KK-LC-1 mRNA between LUAD and adjacent para-cancerous lung tissues. In addition, the association between LUAD and matched normal tissues was also further validated by TCGA.

**Kaplan-Meier potter analysis**

The association between 54,675 genes expression and survival from 21 tumor types can be assessed by Kaplan-Meier potter ([http://kmplot.com](http://kmplot.com)) [19]. We analyzed the prognosis value of KK-LC-1 expression in LUAD. Besides, prognosis of KK-LC-1 expression based on various immune cell were evaluated by Kaplan–Meier plotter. Log-rank $P$-values ($P<0.05$) and hazard ratio (HR) with 95% confidence intervals were computed.

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**Fig. 1** KK-LC-1 expression in various human cancers and related to prognosis in LUAD. **A** Human KK-LC-1 expression in various tumors according to the TIMER database. **B** The expression levels of KK-LC-1 in LUAD and para-cancerous lung tissues. **C** KK-LC-1 expression in LUAD and matched normal tissues by TCGA database. **D** The overall survival rate of KK-LC-1 expression in LUAD.
**TISIDB database analysis**

The TISIDB (http://cis.hku/TISIDB) database is high-throughput screening techniques, molecular profiling, and para-cancerous multiomic data, as well as various resources for immunological data obtained from seven public databases [20]. TISIDB enables analysis of associations between KK-LC-1 and tumor-infiltrating immune cells.

**CIBERSORT algorithm**

CIBERSORT (https://www.biostars.org/p/428905/) is an analytical tool, which aids in evaluating the abundances of member cell types in a mixed cell population through gene expression data [21]. We explored the relationship between high and low expression of KK-LC-1 and 22 types of tumor-infiltrating immune cells using CIBERSORT algorithm.

**Statistical analysis**

R software package was used to analyze TCGA data after download. Statistical analysis was processed by the Statistical Program for Social Sciences (SPSS) 22.0 software (SPSS, Chicago, IL) and GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA). The qRT-PCR data were analyzed using the unpaired Student’s t-test or paired t-test. The Receiver operating characteristic (ROC) curve, and the area under the curve (AUC) were performed to evaluate the diagnostic value of KK-LC-1. The Kaplan-Meier plotter was employed to generate survival curves. Gene expression corrections were performed in the TIMER databases by Spearman’s correlation analysis with the hazard ratio (HR) and P-values or Cox P-values. $P<0.05$ was statistically significant.

**Results**

**The mRNA expression of KK-LC-1 in pan-carcinoma and associated with the prognosis of LUAD**

We firstly analyzed KK-LC-1 expression at the mRNA level, and then explored its prognosis value in patients with LUAD. The differential mRNA expression of KK-LC-1 between diverse tumor tissues and matched para-cancerous tissues was analyzed by TIMER database. KK-LC-1 expression was significantly higher in tumor tissue than matched para-cancerous tissues, including LUAD (Fig. 1A). In a dataset from TCGA, the expression level of KK-LC-1 was

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**Fig. 2** KK-LC-1 expression in serum and related to diagnosis in LUAD. **A** The expression level of KK-LC-1 in LUAD serum and healthy person’s serum. ROC curve of serum **B** KK-LC-1 and **C** CEA. **D** KK-LC-1 expression in LUAD patient’s preoperative and postoperative serum. **E** ROC curve of serum KK-LC-1 to validate pre-operative cases from post-operative in LUAD.
remarkably increased in 538 LUAD tissues compared with 59 normal tissues (Fig. 1B), and the result was consistent with the 59 matched tissue samples from the LUAD patients (Fig. 1C). In addition, we performed a survival analysis in LUAD, which revealed that the higher expression of KK-LC-1 was correlated with a poorer prognosis (Fig. 1D).

The mRNA expression of KK-LC-1 in serum and associated with the diagnosis of LUAD

Next, we evaluated the diagnostic significance of KK-LC-1 in the serum of LUAD patients. The expression level of KK-LC-1 in 92 LUAD patient’s serum was higher than 47 healthy control by qRT-PCR (Fig. 2A). Then, the relationship between the clinicopathological features of LUAD samples and the expression level of KK-LC-1 was analyzed. As shown in Table 1, KK-LC-1 expression was correlated with the stage, Carcino-Embryonic Antigen (CEA), and Neuron-Specific Enolase (NSE) (p < 0.05). The receiver operating characteristic (ROC) curves and the area under curve (AUC) analyses were performed for the diagnostic role of KK-LC-1. Compared with CEA, KK-LC-1 had a higher AUC (0.794 VS. 0.565) (Fig. 2B, C). Interestingly, the expression level of KK-LC-1 in 19 LUAD patients’ serum was significantly decreased than that in patients after operation (Fig. 2D), and KK-LC-1 had a good ability to discriminate distinguish preoperative LUAD cancer patients from and postoperative patients with an AUC of 0.720 (Fig. 2E).

| Clinicopathological factor | n | KK-LC-1 Mean ± SEM | P         |
|----------------------------|---|---------------------|-----------|
| Age (yr)                   |   |                     | 0.5696    |
| < 60                       | 60| 1.571 ± 0.2253      |           |
| ≥ 60                       | 32| 1.793 ± 0.3247      |           |
| Gender                     |   |                     | 0.6368    |
| Male                       | 33| 1.766 ± 0.3441      |           |
| Female                     | 59| 1.583 ± 0.2159      |           |
| Smok                       |   |                     | 0.7261    |
| Yes                        | 7 | 1.405 ± 0.5871      |           |
| No                         | 78| 1.655 ± 0.2057      |           |
| Diameter                   |   |                     | 0.175     |
| < 3                        | 72| 1.627 ± 0.1947      |           |
| ≥ 3                        | 10| 2.472 ± 0.9061      |           |
| Stage                      |   |                     | 0.0087    |
| I                          | 65| 1.340 ± 0.1941      |           |
| II+III+IV                  | 27| 2.392 ± 0.3912      |           |
| CEA                        |   |                     | 0.0416    |
| < 5 ng/ml                  | 75| 1.476 ± 0.1855      |           |
| ≥ 5 ng/ml                  | 13| 2.548 ± 0.6442      |           |
| NSE                        |   |                     | 0.0225    |
| < 16.3 ng/ml               | 41| 1.439 ± 0.2629      |           |
| ≥ 16.3 ng/ml               | 19| 2.641 ± 0.4978      |           |

Association between KK-LC-1 expression and infiltration levels of immune cells in LUAD

We then evaluated the correlation of KK-LC-1 expression with the infiltration levels of immune cells in LUAD based on TIMER database. As shown in Fig. 3A, the expression level of KK-LC-1 was significantly negatively correlated with B cell (r = −0.131, p = 3.81e−03), CD4+ T cell (r = −0.122, p = 7.07e−03), macrophage (r = −0.131, p = 3.85e−03), neutrophil (r = −0.099, p = 3.04e−02), and dendritic cell (r = −0.18, p = 6.48e−05). However, there was no significant correlation between KK-LC-1 and tumor purity (r = −0.043, p = 3.36e−01) and CD8+ T cell (r = −0.04, p = 3.78e−01) (Fig. 3A). This negative correlation between the expression level of KK-LC-1 and CD4+ T cell (r = −0.116, p = 8.29e−03), macrophage (r = −0.1, p = 2.34e−02), Natural killer cell (r = −0.123, p = 5.13e−03), and dendritic cell (r = −0.143, p = 1.15e−03) was found in TISIDB database (Fig. 3B). Next, we further explored the difference between infiltrating immune cells and KK-LC-1 expression by CIBERSORT. The results indicated the higher KK-LC-1 expression related to the higher immune cells infiltration in plasma cell, activated CD4+ memory T cell, follicular helper T cell, macrophages M0, while monocyte, macrophages M2, resting dendritic cell, resting mast cell had opposite result (Fig. 3C).

Association between KK-LC-1 and immune cell type markers

TIMER was used to further investigate the correlation between KK-LC-1 and immune cell markers. After the adjustment for purity, we focused on the immune cell markers of B Cell, T Cell, CD8+ T Cell, Monocyte, M1 Macrophage, M2 Macrophage, TAM, Neutrophil, Natural killer cell, Dendritic cell, and functional T cell markers of Th1, Th2, Thf, Th17, Treg, T cell exhaustion (Table 2). As shown in Table 2 and Fig. 4, KK-LC-1 expression had a remarkable correlation with CD68 and CSF1R of Monocyte (p < 0.05), CD68 and CCL2 of TAM (p < 0.05), NOS2 of M1 Macrophage (p < 0.05), CD163, VSig4 and MS4A4A of M2 Macrophage (p < 0.05). Taken together, KK-LC-1 may be participated in the LUAD immune response by regulating the immune cells.

Prognostic value analysis of KK-LC-1 based on immune cells in LUAD

Finally, we performed prognostic analyses based on KK-LC-1 expression in LUAD in different immune cell
High expression of KK-LC-1 in decreased macrophages cohort in LUAD was associated with better prognosis (Fig. 5H). Meanwhile, high expression of KK-LC-1 in enriched B cells, enriched CD8+ T cells, enriched macrophages, enriched/decreased CD4+ T cells, enriched/decreased natural killer T cells, enriched/decreased regulatory T cells, decreased type 1 T helper cells and enriched/decreased type 2 T helper cells cohorts in LUAD was associated with poor prognosis (Fig. 5A, C-E, G, I-L, N-P). Besides, there was no significant association between low/high KK-LC-1 expression and LUAD patient prognosis in decreased B cells and decreased CD8+ T cells, enriched type 1 T helper cells cohorts (Fig. 5B, F, M). The result suggested that KK-LC-1 expression influenced the prognosis of LUAD patients by directly affecting immune cell infiltration.

**Discussion**
CTAs referred to as CT antigen is expressed only in testis and embryonic primordial cells, but they can also be abnormally expressed in malignant tumors. Previous
### Table 2  Relationship of KK-LC-1 with immune cell type markers by TIMER database

| Description          | Marker genes | None Cor | P    | Purity Cor | P    |
|----------------------|--------------|----------|------|------------|------|
| B Cell               | CD19         | 0.097    | *    | 0.088      | 0.052|
|                      | CD79A        | 0.095    | *    | 0.079      | 0.081|
| T Cell (general)     | CD3D         | 0.019    | 0.672| −0.016     | 0.722|
|                      | CD3E         | −0.013   | 0.761| −0.054     | 0.229|
|                      | CD2          | −0.037   | 0.403| −0.082     | 0.068|
| CD8+ T Cell          | CD8A         | 0.04     | 0.36 | 0.015      | 0.738|
|                      | CD8B         | 0.03     | 0.501| 0.009      | 0.837|
|                      | CD45(PTPRC)  | −0.099   | *    | −0.146     | **   |
| Monocyte             | CD66         | −0.083   | 0.061| −0.129     | **   |
|                      | CD11S(CSF1R) | −0.171   | ***  | −0.215     | ***  |
| M1 Macrophage        | iNOS (NOS2)  | 0.123    | **   | 0.114      | *    |
|                      | IRF5         | −0.016   | 0.721| −0.202     | 0.516|
|                      | COX2(PGTS2)  | 0.065    | 0.14 | 0.058      | 0.196|
| M2 Macrophage        | CD163        | −0.08    | 0.069| −0.114     | *    |
|                      | VSIG4        | −0.126   | **   | −0.158     | ***  |
|                      | M54A4A       | −0.107   | *    | −0.143     | **   |
| TAM                  | CD68         | −0.08    | 0.071| −0.111     | *    |
|                      | IL10         | −0.052   | 0.243| −0.068     | 0.13 |
|                      | CCL2         | −0.073   | 0.097| −0.092     | *    |
| Neutrophil           | CD66b (CEACAM8)| −0.169 | ***  | −0.186     | ***  |
|                      | CD15(FUT4)   | 0.094    | *    | 0.101      | *    |
|                      | CCR7         | −0.03    | 0.493| −0.061     | 0.173|
| Natural killer cell  | KIR2DL1      | 0.008    | 0.849| −0.008     | 0.854|
|                      | KIR2DL3      | 0.034    | 0.447| 0.026      | 0.0572|
|                      | KIR2DL4      | 0.142    | **   | 0.135      | **   |
|                      | KIR3DL1      | 0.087    | *    | 0.089      | *    |
|                      | KIR3DL2      | 0.047    | 0.288| 0.045      | 0.318|
|                      | KIR3DL3      | 0.116    | 0.087| 0.116      | **   |
|                      | KIR2DS4      | 0.024    | 0.585| 0.022      | 0.623|
| Dendritic cell       | BDCA-1 (CD1c)| −0.214   | ***  | −0.238     | ***  |
|                      | BDCA-3 (THBD)| −0.16    | ***  | −0.175     | ***  |
|                      | BDCA-4 (NRPI)| −0.032   | 0.472| −0.036     | 0.426|
|                      | CD11c (ITGAX)| −0.053   | 0.227| −0.088     | 0.051|
| Th1                  | T-bet (TBX21)| −0.024   | 0.582| −0.047     | 0.293|
|                      | STAT4        | −0.014   | 0.752| −0.046     | 0.309|
|                      | TNF-α (TNF)| −0.061   | 0.169| −0.084     | 0.062|
|                      | STAT1        | 0.065    | 0.143| 0.046      | 0.306|
| Th2                  | GATA3        | −0.031   | 0.483| −0.073     | 0.105|
|                      | STAT5A       | −0.122   | **   | −0.152     | ***  |
|                      | STAT6        | −0.027   | 0.534| −0.033     | 0.465|
| Th17                 | BC1L6        | 0.021    | 0.641| 0.017      | 0.714|
|                      | IL21         | 0.047    | 0.292| 0.021      | 0.641|
| Treg                 | STAT3        | 0.029    | 0.516| 0.03       | 0.454|
|                      | IL17A        | 0.055    | 0.214| 0.05       | 0.266|
|                      | FOXP3        | 0.015    | 0.738| −0.025     | 0.582|
|                      | CD25(IL2RA)  | −0.026   | 0.553| −0.059     | 0.195|
|                      | CCR8         | 0.007    | 0.882| −0.082     | 0.542|
|                      | TGFβ (TGFBI)| −0.064   | 0.167| −0.075     | 0.095|
|                      | STAT3B       | −0.021   | 0.659| −0.01      | 0.828|
researches showed that CTAs were involved in the occurrence and development of tumors [22]. CTA can be used as an immunotherapy target mediated by cytotoxicity T lymphocyte [23]. Some CTAs were identified to have immunogenicity, indicating the possibility of tumor immunotherapy targets [24–26]. In previous studies, compared with NY-ESO-1 (10.5%), which has been used in clinical immunotherapy, KK-LC-1 (32.6%) has a higher expression level in NSCLC [27]. KK-LC-1 also has been reported that be highly expressed in lung cancer, gastric cancer, triple-negative breast cancer (TNBC), and hepatocellular carcinoma (HCC) [12, 13, 28, 29]. In this study, we determined the database-derived tissues and clinic-derived serum expression levels of KK-LC-1 in LUAD patients, and analyzed the correlation of KK-LC-1 with immune cell infiltration of LUAD.

When KK-LC-1 was first discovered, it was positively expressed in 50% of 15 lung cancer cell lines and 38% of LUAD tissues [12]. Hsu et al. reported that KK-LC-1 expression level was higher in LUAD than LUSC [30]. The expression of KK-LC-1 was intimately related to tumor stage and lymph node metastasis in lung cancer patients [31]. Our results from TIMER and TCGA databases showed that KK-LC-1 expression was up-regulated in LUAD tissues compared with normal tissues. Meanwhile, high levels of expression of KK-LC-1 were also closely correlated with poor overall survival, suggesting that KK-LC-1 may be a promising biomarker for survival prediction in LUAD. The above results only focus on the expression of KK-LC in tissue and cells but not in serum or plasma. As we all known, compared with tissue samples, serum has the advantages of being less invasive, easy to obtain and repeatable. In our study, it was the first time to analyze KK-LC-1 expression in serum from LUAD patients. As expected, serum KK-LC-1 expression was remarkably decreased...
after surgery, indicating serum KK-LC-1 was closely correlated with tumor occupying. These findings implied that serum KK-LC-1 could serve as a tumor marker for a diagnostic and prognostic predictor in LUAD patients.

Paret et al. demonstrated that KK-LC-1 could induce a strong antigen-specific immune response in TNBC based on specific recognition of TCR epitopes through vitro and vivo experiments [32]. Marcinkowski et al. also reported that KK-LC-1 has great potential in T cell receptor (TCR) gene-engineered T cells therapy for gastric cancer [33]. These evidences suggested that KK-LC-1 might be a progressing immunotherapy target. In our study, we found that KK-LC-1 was negative correlated with immune cell infiltration CD4+ T cell, macrophage, neutrophil and dendritic cell, which was further validated by immune cell surface markers. It is well known that CD4+ T cell, macrophage, neutrophil and dendritic cell play antitumor roles in cancers [34–36]. The negative correlation between KK-LC-1
and immune cells further indicated that KK-LC-1 seemed to play a important role in promoting cancer. At the same time, KK-LC-1 directly affected patient outcomes by influencing immune cell infiltration, which was similar with the research by Yoshinobu Ichiki et al. in LUSC [14]. Hsu et al. also reported that KK-LC-1 was related to the abundance of macrophages and CD4+ T cells through QuantiSeq algorithm in lung cancer [30]. Our results showed that KK-LC-1 expression level was strongly correlated with lung cancer-related immune cells infiltration, and KK-LC-1 affected the prognosis of LUAD by modulating the infiltration level of tumor infiltrating immune cells (TIICs).

However, the research on relevant mechanisms is limited in our study. In fact, to date, there are few reports on the mechanism of KK-LC-1 in human malignant tumors. Methylated CpG islands associated with the CT genes in normal somatic cells become demethylated in cancer cells, indicating activation of their expression. Xie et al. reported that PIWI1 is considered to be a highly expressed CT gene in LUAD, and promoter DNA hypomethylation of PIWI1 could contribute to its aberrant expression in LUAD [37]. KK-LC-1 expression is activated by treatment with the hypomethylating agent 5-aza-2’-deoxycytidine in KK-LC-1 negative breast cancer cell lines [15, 32].

To sum up, the high expression level of serum KK-LC-1 in patients with LUAD was closely related to TNM stage, CEA and NSE. The expression of serum KK-LC-1 mRNA decreased significantly after surgery. KK-LC-1 expression has a strong correlation with lung cancer-related immune cells infiltration, which can affect the prognosis of LUAD. Our findings suggest that KK-LC-1 played a non-redundant role in tumor immunology and served as a diagnostic biomarker in LUAD. However, it needs a further study to verify the above results with large sample size, and to explore the mechanisms and immunoregulatory functions of KK-LC-1 in LUAD.

**Conclusions**

KK-LC-1 may serve as a promising diagnostic and prognostic biomarker in LUAD and is correlated with immune infiltration and prognosis.

**Acknowledgements**

We thank the Fujian Provincial hospital for providing experimental support for this study.

**Authors’ contributions**

Yanli Kang and Yuhang Gan performed the bioinformatics analysis, drafted the manuscript and prepared the figures. Yingfeng Jiang, Jianbin You, Chen Huang, Qianshun Chen and Xunyu Xu collected the related references and participated in discussion. Liangyuan Chen and Falin Chen made substantial contributions to conception and design of the research. All authors contributed to this manuscript. The author(s) read and approved the final manuscript.

**Funding**

This work was supported by the Medical Innovation Grant of Fujian Province (No.2019-CXB-1); Fujian Natural Science Foundation of China (No. 2021 J1375).

**Availability of data and materials**

The data, which was used in this study can be found at the following websites and thoracic surgery, Fujian Provincial Hospital. All methods were carried out in accordance with relevant guidelines and regulations. The differentially expressed in Pan-cancer was analyzed by TIMER (https://cistrome.shinyapps.io/timer/) and TCGA databases (http://portal.gdc.cancer.gov/). The Kaplan-Meier potter (http://kmplot.com) was utilized to evaluated prognosis. The association between KK-LC-1 and immune infiltration was explored by TIMER and TISIDB database (http://cis.hku.hk/TISIDB), and CIBERSORT (https://www.biostars.org/p/428905/) algorithm. The datasets used during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Research Ethics Committee of Fujian Provincial Hospital (K-2021-040-04) and conformed to the ethical standards of the 1964 Helsinki Declaration, and all subjects and voluntarily signed informed consent forms.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that have no competing interests.

**Received:** 12 April 2022   **Accepted:** 25 July 2022

**Published online:** 30 July 2022

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