The expression landscape of JAK1 and its potential as a biomarker for prognosis and immune infiltrates in NSCLC

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Introduction
Lung cancer, as a malignant tumour with high morbidity and mortality, poses a serious threat to people’s physical and mental health [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases [2]. With the advent of precision...
therapy, lung cancer treatment has entered molecular therapy, including targeted therapy, anti-angiogenesis therapy and immunotherapy [3]. However, the prognosis has not improved significantly, and the 5-year survival rate remains poor [1]. In recent years, clinical studies have shown that immunotherapy (PD-1/L1 monoclonal antibody, CTLA-4 inhibitor) has great potential in the treatment of lung cancer patients without epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations [4]. Nevertheless, immunotherapy only activates immune cells in a subset of patients. With the continuous exploration of the tumour immune microenvironment (TME), which can directly or indirectly affect the development of tumours, including promoting tumour angiogenesis, changing the biological characteristics of the tumour, promoting immune escape, and even regulating the activity of cancer stem cells (CSCs) [5, 6]. Many studies have found that TAMs (tumour-associated macrophages), TILs (tumour infiltrating lymphocytes) and TINs (tumour-infiltrating neutrophils) in the TME can affect the efficacy of immunotherapy [7, 8]. Hence, it is imperative to find immune infiltration-related biomarkers that are related to the prognosis of NSCLC.

Janus-activated kinase (JAK) is an inactive tyrosine protein kinase that consists of four family members, including JAK1, JAK2, TYK2, and JAK3 [9]. JAKs approach each other and are activated by interactive tyrosine phosphorylation, ultimately leading to signal transducer and activator of transcription (STAT) proteins forming a homo/heterodimer that is incorporated into the nucleus and binding to the target gene promoter to activate transcription and expression [10]. Previous studies have shown that the JAK1/STAT3 pathway is widely involved in many significant biological processes, such as cell proliferation, differentiation, apoptosis and immune regulation [11–13]. JAK family kinases play an essential role in cytokine signalling. Functionally acquired JAK1 mutations can encourage the development of cancers, especially leukaemia. Abnormal JAK1 expression either promotes or suppresses tumour growth [10, 14, 15]. Chen et al. [10] showed that high expression of JAK1 mRNA was associated with TNM (Tumor, Node, Metastasis) stage and superior prognosis of breast cancer. In addition, infiltration and enrichment of immunoregulatory cells were significantly positively correlated with JAK1 expression. In contrast, Zhang et al. [16] showed that JAK1 signal activation could promote the proliferation of bladder cancer cells and lead to a poor prognosis. Hu et al. also indicated that JAK1/STAT3 plays a crucial role in ovarian cancer as a pro-oncogenic signalling pathway [17]. Whether JAK1 expression is involved in the prognosis and the level of immune infiltration in NSCLC still needs to be further explored.

In our descriptive study, we explored the expression landscape of JAK1 in NSCLC and its relationship with prognosis using shared databases, including TIMER, GEPIA, Kaplan–Meier Plotter and PrognoScan. We also visualized the relationship between JAK1 and immune infiltration using TIMER and TISIDB. Moreover, correlations between JAK1 expression and multiple gene marker sets related to immune infiltrates were also analysed via TIMER and GEPIA.

**Materials and methods**

**TIMER database analysis**
The TIMER (Tumour Immune Estimation Resource) web server is a comprehensive resource for the systematic analysis of immune infiltrates across diverse cancer types.
(https://cistrome.shinyapps.io/timer/) [18]. The abundances of six immune infiltrates (B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells) were estimated by the TIMER algorithm. We evaluated the correlation between JAK1 expression levels and various immune infiltrating cells via the TIMER algorithm. In addition, JAK1 expression profiles across various tumour samples and paired normal tissues from the TCGA data in TIMER were also determined. Finally, to further identify other potential subtypes of immune cell infiltration, we also analysed the correlation between JAK1 expression and diverse immune cell markers, including monocytes, tumour-associated macrophages (TAMs), M1 macrophages, M2 macrophages, CD8+ T cells, B cells, neutrophils, dendritic cells, natural killer (NK) cells, T-helper 1 (Th1) cells, T-helper 2 (Th2) cells, Tregs and exhausted T cells (https://www.rndsystems.com/cn/resources/cell-markers/immune-cells). Tumour purity was also determined. The gene expression level was described in terms of log_TAM. JAK1 expression was drawn in the x-axis, while marker genes were drawn in the y-axis. A scatterplot was used to describe the specific connection between every immune gene marker and JAK1 expression.

TISIDB analysis

TISIDB is also a web portal for tumour and immune system interaction, which integrates multiple heterogeneous data types. (http://cis.hku.hk/TISIDB/index.php) [19]. We explored the correlation between JAK1 expression in NSCLC and the abundance of multiple immune cells, including activated CD4 T cells (Act_CD4), activated dendritic cells (Act_DCs), immature dendritic cells (iDCs), neutrophils, natural killer (NKs), plasmacytoid dendritic cells (pDCs), central memory CD4 cells (Tcm_CD4), and effector memory CD8 cells (Tem_CD8). The relative abundance of each immune cell was inferred by using gene set variation analysis (GSVA) based on the gene expression profile. JAK1 expression was drawn on the x-axis, while the abundance of immune cells was drawn on the y-axis. A scatterplot was used to display the correlation between the abundance of each immune cell and JAK1 expression.

GEPIA database analysis

To further verify the gene marker associated with immune infiltration in NSCLC. We used the public database Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/index.html) [20], which analyses the RNA sequencing expression from the TCGA and GTEx projects of 9736 tumours and 8587 normal samples. The correlation coefficient was determined by the Spearman method. The tumour and normal tissue datasets were used for analysis. JAK1 expression profiles across LUAD (lung adenocarcinoma) and LUSC (lung squamous cell carcinoma) samples and paired normal tissues from GEPIA were also analysed.

Prognostic analysis

We used public databases including Kaplan–Meier Plotter (https://kmplot.com/analysis/) [21] and PrognoScan (http://dna00.bio.kyutech.ac.jp/PrognoScan/index.html) [22] to examine the relationship between JAK1 expression level and NSCLC prognosis. The Kaplan–Meier plotter is competent for assessing the effect of 54,000 genes on prognosis in 21 cancer types. Sources included the GEO, EGA, and TCGA databases. The hazard
ratio (HR) and its 95% confidence interval (95% CI) for OS (overall survival) and PFS (progression-free survival) in NSCLC were calculated. The log-rank \( P \) value was likewise computed.

Similarly, the prognostic database PrognoScan was designed to analyse the correlation between JAK1 expression and overall survival (OS). The threshold was set as a Cox \( P \) value < 0.05.

**Statistical analysis**

The results examined in TIMER and GEPIA are displayed with \( P \) values determined by \( t \) tests, fold changes, and gene ranks. Survival outcomes were presented with Kaplan–Meier plots and PrognoScan, and the results are displayed with HR and Cox \( P \) values from a log-rank test. The correlation between JAK1 expression and each gene marker was assessed by Spearman’s correlation test and statistical significance. The strength of the correlation was defined as follows: 0.00–0.19 “very weak”, 0.20–0.39 “weak”, 0.40–0.59 “moderate”, 0.60–0.79 “strong”, and 0.80–1.0 “very strong”. For all analyses, a \( P \) value less than 0.05 indicates statistical significance.

**Results**

**JAK1 expression in multiple human tumours**

We evaluated the differences in JAK1 expression in various human tumour tissues and paired normal tissues using RNA sequencing data from the TCGA. The detailed expression of JAK1 in the tumour and adjacent tissues is shown in Fig. 1A. JAK1 expression was significantly decreased in BLCA (bladder urothelial carcinoma), BRCA (breast invasive carcinoma), COAD (colon adenocarcinoma), KICH (kidney chromophobe), LUAD, LUSC, PRAD (prostate adenocarcinoma), READ (rectum adenocarcinoma), and UCEC (uterine corpus endometrial carcinoma) compared to that in adjacent normal tissues, while the expression of JAK1 was significantly higher in CHOL (cholangiocarcinoma), ESCA (oesophageal carcinoma), HNSC (head and neck squamous cell carcinoma), KIRC (kidney renal clear cell carcinoma), KIRP (kidney renal papillary cell carcinoma), LIHC (liver hepatocellular carcinoma), STAD (stomach adenocarcinoma), and THCA (thyroid carcinoma) than that in adjacent normal tissues.

![Fig. 1](image-url)
To further evaluate the expression patterns of JAK1 in NSCLC, the GEPIA database was further selected. Similar results were likewise obtained, namely, JAK1 expression in LUAD and LUSC was significantly lower than that in the paired normal tissues (Fig. 1B).

**JAK1 expression predicts the prognosis of NSCLC**

Next, we explored the prognostic value of JAK1 for NSCLC by adopting two public databases. First, we investigated JAK1 expression and the prognosis of NSCLC, LUAD and LUSC using Kaplan–Meier Plotter, which principally focused on the strength of the information from the GEO, EGA and TCGA miRNA gene chips. The results showed that high JAK1 expression indicated a favourable prognosis in NSCLC (OS: HR, 0.62, 95% CI from 0.53 to 0.74, log-rank \( P < 0.001 \); PFS: HR, 0.65, 95% CI from 0.50 to 0.86, log-rank \( P = 0.002 \)). In the subgroup analysis, the high expression of JAK1 in LUAD lasted longer in OS (HR: 0.74, 95% CI from 0.58 to 0.95, log-rank \( P = 0.017 \)), but there was no benefit in PFS (HR: 0.83, 95% CI from 0.60 to 1.14, log-rank \( P = 0.24 \)). In LUSC, high expression of JAK1 was associated with longer duration of PFS (HR: 0.65, 95% CI from 0.39 to 1.09, log-rank \( P = 0.097 \)), while the difference was not statistically significant. In addition, there was no benefit in OS (HR: 0.95, 95% CI from 0.69 to 1.29, log-rank \( P = 0.73 \)). (Fig. 2).

Next, we investigated the association of JAK1 expression and prognosis with distinct clinicopathological features in NSCLC (Table 1). JAK1 overexpression related to superior OS and PFS in males (HR: 0.64, 0.62, 95% CI from 0.52 to 0.79, \( P < 0.001 \)) rather than females. In addition, the higher expression of JAK1 is associated with preferable OS in patients with N2 lymph node metastasis (HR: 0.39, 95% CI from 0.17 to 0.86, \( P = 0.016 \)).

![Fig. 2 Kaplan–Meier survival curves comparing high and low expression of JAK1 in NSCLC. A, B OS and PFS survival curves of NSCLC (n = 1144, n = 596). C, D OS and PFS survival curves of LUAD (n = 672, n = 443). E, F OS and PFS survival curves of LUSC (n = 271, n = 141). OS overall survival, PFS progression-free survival, LUAD lung adenocarcinoma, LUSC lung squamous cell carcinoma, NSCLC non-small-cell lung cancer, HR hazard ratio.](image-url)
without distant metastasis (HR: 0.73, 95% CI from 0.56 to 0.93, \(P=0.013\)) of NSCLC. Notably, overexpression of \(JAK1\) is associated with undesirable prognosis in patients with stage 1 NSCLC (OS: HR, 1.46, 95% CI from 1.06 to 2.00, \(P=0.02\)) and without lymph node metastasis (PFS: HR, 2.18, 95% CI from 1.06 to 4.46, \(P=0.029\)), which implicit early NSCLC patients with \(JAK1\) overexpression may have a poor prognosis. Regrettably, there were no statistically significant differences between \(JAK1\) expression and prognosis in females, stage 2 to 3, stage T1 to T4, N1 lymph node metastasis or prior chemotherapy. The exact survival time is shown in Additional file 1: Table S1.

Finally, we selected the PrognoScan database to further verify the relationship between \(JAK1\) expression and prognosis in NSCLC. Five cohorts containing a total of 530 patients with NSCLC and LUAD showed that high expression of \(JAK1\) was associated with favourable OS (Table 2).

### Correlation of \(JAK1\) expression and immune infiltration

Tumour infiltrating lymphocytes (TILs) are closely related to prognosis and subsequent immunotherapy in lung cancer [23, 24]. We investigated the correlation between \(JAK1\) expression level and immune cell infiltration in LUAD and LUSC.
from TIMER. The results showed that JAK1 expression was negatively correlated with tumour purity ($r = -0.229$, $P = 2.73e-07$) and significantly positively correlated with infiltrating levels of B cells, CD8$^+$ T cells, CD4$^+$ T cells, macrophages, neutrophils, and dendritic cells in LUAD. JAK1 expression was negatively correlated with tumour purity and significantly positively correlated with infiltrating levels of B cells, CD8$^+$ T cells, CD4$^+$ T cells, macrophages, neutrophils, and dendritic cells in LUSC. What needs illustration is that JAK1 expression has

Table 2 Survival analysis of JAK1 mRNA in NSCLC from the PrognoScan database

| Dataset       | Subtype | Endpoint | Number | Ln (HR-high/HR-low) | COX P value | Ln HR | HR [95% CI low上限] |
|---------------|---------|----------|--------|----------------------|-------------|-------|---------------------|
| jacob-00182-CANDF | LUAD    | OS       | 82     | −1.11                | 0.002460    | −1.37 | 0.25 [0.10–0.62]    |
| GSE31210      | LUAD    | OS       | 204    | −1.18                | 0.026306    | −1.13 | 0.32 [0.12–0.88]    |
| GSE11117      | NSCLC   | OS       | 41     | −1.55                | 0.034669    | −0.78 | 0.46 [0.22–0.95]    |
| MICHIGAN-LC   | LUAD    | OS       | 86     | −1.25                | 0.094138    | −0.85 | 0.43 [0.16–1.16]    |
| GSE13213      | LUAD    | OS       | 117    | −0.73                | 0.057336    | −0.43 | 0.65 [0.42–1.01]    |

Fig. 3 TIMER database showing the relationship between JAK1 expression level and immune infiltration in LUAD and LUSC. A JAK1 expression was negatively correlated with tumour purity and significantly positively correlated with infiltrating levels of B cells, CD8$^+$ T cells, CD4$^+$ T cells, macrophages, neutrophils, and dendritic cells in LUAD. B JAK1 expression was negatively correlated with tumour purity and significantly positively correlated with infiltrating levels of B cells, CD8$^+$ T cells, CD4$^+$ T cells, macrophages, neutrophils, and dendritic cells in LUSC. LUAD lung adenocarcinoma, LUSC lung squamous cell carcinoma. A $P$ value less than 0.05 indicated statistical significance
no significant corrections with infiltrating levels of Act_CD4 in LUSC. For details, please refer to Fig. 4 and Additional file 1: Fig S1.

**Correlations between JAK1 expression and immune gene markers**

To further understand the interaction between JAK1 expression and TME in NSCLC, we further explored the potential correlation between JAK1 and immune gene markers in the public databases TIMER and GEPIA (Tables 3, 4). These gene markers depicted diverse immune infiltration cells, including monocytes, TAMs, M1 macrophages, M2 macrophages, CD8\(^+\) T cells, B cells, neutrophils, dendritic cells and NK cells. In addition, various T cells, including Th1, Th2, Tregs, and T cell exhaustion, which play different functions in the TME, were included. Although they were adjusted for tumour purity, most immune markers remained significantly related to JAK1 expression levels in LUAD and LUSC.

Interestingly, the results from TIMER and GEPIA showed that most gene sets of monocytes, M1 macrophages, and TAMs were significantly associated with JAK1 expression levels in LUAD. However, we discovered that JAK1 expression was also associated with most gene sets of monocytes and TAMs rather than M1 macrophages. Notably, the majority chemokine ligand, which induced cells of the immune system to enter the site of infection, CCL-2, CD80 and CD68 of TAMs, IRF5 and NOS2 of M1, CD163 and MS4A4A of M2 were strongly related to JAK1 expression in LUAD (all \(P\) value < 0.0001). These consequences suggest that JAK1 may play a vital role in the TME by regulating the function of macrophages. In addition, some of the gene markers, such as MPO, CCR7 and CD11b (ITGAM), of neutrophils and CD8A of CD8\(^+\) T cells were associated with JAK1 expression in LUAD and LUSC.
Table 3  Correlation analysis between JAK1 and diverse immune gene markers in LUAD and LUSC from the TIMER database

| Description     | Gene markers | LUAD |       | P     | LUSC |       | P     |
|-----------------|--------------|------|-------|-------|------|-------|-------|
|                 |              | None |       |       | None |       |       |
| Monocyte        | CD14         | 0.262 | ***   | 0.2   | 0.425 | ***   | 0.323 | ***   |
|                 | CSF1R        | 0.503 | ***   | 0.463 | ***   | 0.553 | ***   | 0.482 | ***   |
|                 | CD86         | 0.395 | ***   | 0.344 | ***   | 0.444 | ***   | 0.349 | ***   |
| TAM             | CCL2         | 0.254 | ***   | 0.19  | ***   | 0.368 | ***   | 0.296 | ***   |
|                 | CD80         | 0.385 | ***   | 0.331 | ***   | 0.383 | ***   | 0.294 | ***   |
|                 | CD68         | 0.383 | ***   | 0.339 | ***   | 0.382 | ***   | 0.29  | ***   |
| M1              | IRF5         | 0.323 | ***   | 0.277 | ***   | 0.068 | 0.126 | 0.049 | 0.281 |
|                 | NOS2         | 0.22  | ***   | 0.194 | ***   | 0.062 | 0.165 | 0.071 | 0.122 |
| M2              | CD163        | 0.45  | ***   | 0.414 | ***   | 0.458 | ***   | 0.378 | ***   |
|                 | ARG1         | 0.113 | *     | 0.11  | 0.015 | −0.069 | 0.125 | −0.074 | 0.107 |
|                 | MS4A4A       | 0.352 | ***   | 0.3   | 0.345 | ***   | 0.24  | ***   |
| CD8+ T cell     | CD8A         | 0.248 | ***   | 0.177 | ***   | 0.262 | ***   | 0.175 | **    |
|                 | CD8B         | 0.118 | *     | 0.051 | 0.257 | 0.188 | 0.035 | *     |
| B cell          | CD19         | 0.121 | *     | 0.02  | 0.653 | 0.277 | 0.146 | *     |
|                 | CD79A        | 0.137 | *     | 0.047 | 0.295 | 0.323 | 0.198 | ***   |
| Neutrophils     | CEACAM8      | 0.259 | ***   | 0.252 | ***   | 0.072 | 0.106 | 0.048 | 0.293 |
|                 | MPO          | 0.22  | ***   | 0.183 | ***   | 0.342 | ***   | 0.29  | ***   |
|                 | CCR7         | 0.361 | ***   | 0.295 | ***   | 0.39  | ***   | 0.291 | ***   |
|                 | CD11b(ITGAM)| 0.472 | ***   | 0.435 | ***   | 0.578 | ***   | 0.517 | ***   |
| Dendritic cell  | HLA-DPB1     | 0.313 | ***   | 0.249 | ***   | 0.457 | ***   | 0.371 | ***   |
|                 | HLA-DQB1     | 0.253 | ***   | 0.192 | ***   | 0.328 | ***   | 0.245 | ***   |
|                 | HLA-DRA      | 0.281 | ***   | 0.215 | ***   | 0.387 | ***   | 0.292 | ***   |
|                 | HLA-DPA1     | 0.353 | ***   | 0.3   | ***   | 0.454 | ***   | 0.371 | ***   |
|                 | BDCA-1(CD1C)| 0.294 | ***   | 0.243 | ***   | 0.341 | ***   | 0.227 | ***   |
|                 | BDCA-4(NRP1)| 0.386 | ***   | 0.377 | ***   | 0.523 | ***   | 0.473 | ***   |
|                 | CD11c(ITGAX)| 0.383 | ***   | 0.327 | ***   | 0.513 | ***   | 0.427 | ***   |
|                 | CD141(THBD)| 0.366 | ***   | 0.344 | ***   | 0.032 | 0.469 | −0.006 | 0.89 |
| NK cell         | KIR2DL1      | 0.046 | 0.296 | 0.023 | 0.612 | 0.143 | *     | 0.091 | 0.047 |
|                 | KIR2DL3      | 0.104 | 0.019 | 0.06  | 0.187 | 0.158 | **    | 0.117 | 0.010 |
|                 | KIR2DL4      | 0.062 | 0.163 | 0.015 | 0.737 | 0.113 | 0.011 | 0.051 | 0.265 |
|                 | KIR3DL1      | 0.064 | 0.15  | 0.024 | 0.601 | 0.241 | ***   | 0.187 | ***   |
|                 | KIR3DL2      | 0.139 | *     | 0.087 | 0.053 | 0.141 | *     | 0.069 | 0.134 |
|                 | KIR3DL3      | 0.002 | 0.964 | −0.019 | 0.67 | 0.029 | 0.52  | 0.002 | 0.962 |
|                 | KIR2DS4      | 0.119 | *     | 0.082 | 0.068 | 0.122 | *     | 0.093 | 0.043 |
|                 | CD7          | 0.168 | **    | 0.091 | 0.043 | 0.339 | 0.237 | ***   |
|                 | XCL1         | 0.036 | 0.416 | 0.004 | 0.931 | −0.015 | 0.742 | 0.017 | 0.705 |
| Th1             | T-bet (TBX21) | 0.322 | ***   | 0.263 | ***   | 0.363 | ***   | 0.273 | ***   |
|                 | STAT4        | 0.336 | ***   | 0.274 | ***   | 0.49  | ***   | 0.415 | ***   |
|                 | STAT1        | 0.398 | ***   | 0.364 | ***   | 0.298 | ***   | 0.251 | ***   |
|                 | IFN-γ (IFNG)| 0.129 | *     | 0.06  | 0.181 | 0.121 | *     | 0.057 | 0.216 |
|                 | TNF-α (TNF) | 0.271 | ***   | 0.229 | ***   | 0.402 | ***   | 0.345 | ***   |
| Th2             | GATA3        | 0.435 | ***   | 0.387 | ***   | 0.551 | ***   | 0.517 | ***   |
|                 | STAT6        | 0.293 | ***   | 0.318 | ***   | 0.265 | ***   | 0.284 | ***   |
|                 | STAT5A       | 0.53  | ***   | 0.495 | ***   | 0.549 | ***   | 0.491 | ***   |
|                 | IL13         | 0.079 | 0.072 | 0.032 | 0.479 | 0.152 | **    | 0.083 | 0.072 |
Moreover, the vast majority of gene sets of dendritic cells, including HLA-DPB1, HLA-DQB1, HLA-DRA, HLA-DPA1, BDCA-1, BDCA-4 and CD11C, were positively correlated with JAK1 expression levels in LUAD and LUSC. These results indicated that LAYN may regulate DCs to play a major role in the TME. Regretfully, nearly all of the gene markers of NK cells had no correlation with JAK1 expression levels. Furthermore, we investigated the relationship between JAK1 expression and gene sets of Tregs and T cell exhaustion. All gene sets suggested a positive correlation with JAK1
expression. Finally, immune checkpoints such as PD-1, CTLA-4, LAG3 and TIM3 were strongly connected with the level of JAK1 expression, which suggested that JAK1 may play a role in immunotherapy for NSCLC. Further molecular biology experiment verification is needed.

Discussion

The JAK1/STAT signalling pathway, as a stimulant that is intimately related to the physiological function of interferon, plays a significant role in cell growth, differentiation, immune regulation and other aspects [11, 25, 26]. The exhaustive function of JAK1 in NSCLC has not yet been clarified. Here, we report the expression profile of JAK1 and its association with prognosis and immune infiltration in NSCLC. We found that JAK1 was expressed at low levels in NSCLC, and its expression level was positively correlated with the prognosis of NSCLC, especially in LUAD. Interestingly, JAK1 overexpression was associated with preferable survival in males, stage N2 patients and patients without distant metastasis. In addition, increased levels of JAK1 expression are associated with undesirable survival in patients with earlier stages (stage 1 and N0), suggesting that early-stage NSCLC patients with JAK1 overexpression may have a bleak prognosis. Moreover, diverse immune infiltration cells and gene sets were positively correlated with JAK1 expression level. Hence, to the best of our knowledge, our study is the first to reveal the potential mechanism by which JAK1 functions in the TME and acts as a prognostic biomarker of NSCLC.

The TME plays a crucial role in the gene expression and clinical efficacy of tumour tissues, which are prerequisites and guarantees tumour immune escape [27]. The TME refers to the sum of various immune-related factors, mainly consisting of immune cells and immune-related molecules. In our study, we found that JAK1 expression was significantly positively correlated with the infiltration of various immune cells (monocytes, neutrophils, B cells, dendritic cells, TAMs) in LUAD and LUSC. Presently, the antitumour function of manifold cells has been extensively recognized, especially CD8+ T cells [28], whose number reflects the immune system's ability to kill tumour cells to some extent. Moreover, CD8+ T cell density was positively correlated with the efficacy of immune checkpoint inhibitors (ICIs) in NSCLC and melanoma [29, 30]. This finding may provide an early indication for the efficacy of immunotherapy for NSCLC.

Another significant part of our study is that diverse gene sets were positively correlated with JAK1 expression levels. First, M1 macrophage-related gene markers, such as IRF5 and NOS2, and the gene marker CD163 of M2 macrophages were strongly correlated with JAK1 expression. These findings suggested that JAK1 may play a role in regulating TAM polarization in the TME. Second, overexpression of JAK1 is associated with a variety of T helper cells (Th1, Th2). This intense correlation may indicate that JAK1 regulates T cell function in the immune microenvironment of NSCLC. Third, our study showed a significant correlation between Treg activation (FOXP3, STAT5B, TGFB1, CCR8, CD25 in LUAD and LUSC) and induced T cell exhaustion (PD-1, CTLA-4, TIM-3 in LUAD and LUSC) and JAK1 overexpression. PD-1 (programmed death receptor 1) is a vital immunosuppressive molecule expressed on the surface of T cells that regulates the immune system and promotes tolerance by downregulating the immune system's
response to human cells and by suppressing the inflammatory activity of T cells [31]. Additionally, CTLA-4 and Tim-3 are expressed on regulatory T cells and exhausted T cells as crucial receptor proteins, respectively [32, 33], and both are significantly positively correlated with JAK1 expression. These results suggest that JAK1 plays a potential role in recruiting immune-infiltrating cells in the TME of NSCLC.

Recent studies provide possible mechanisms which explains why JAK1 overexpression correlates with immune infiltration and superior prognosis. Previous studies have shown that JAK1 overexpression can lead to the activation of downstream interferon-stimulated genes, which can eventually exert a range of antitumour effects [34, 35]. These include increased antigen presentation by inducing proteasome subunits, activating transporters associated with antigen processing (TAP), stimulating major histocompatibility complex (MHC) molecules to be involved in antigen recognition and promoting chemokine production to exploit a first-hand antitumour role [36]. Remarkably, numerous studies have revealed that loss-of-function JAK1 mutations are insinuative of immune evasion [11, 37, 38]. Research by Shin et al. [35] showed that JAK1 mutations could induce primary resistance to PD-1 inhibitors in melanoma and colon cancer patients. Rodig et al. [39] also indicated that loss of JAK1 caused perinatal death in mice. Luo et al. [40] have shown that the response of melanoma to PD-L1 inhibitor immunotherapy requires JAK1 signaling, which may be related to its potentiated IFN-γ response in vivo and in vitro. Besides, researchers also point out that human melanoma cell lines are insensitive to interferon (IFN)-induced antitumor effects after JAK1/2 knockout [41]. Consequently, JAK1 may regulate immune-related pathways that affect the prognosis and immune infiltrates of NSCLC. Concrete mechanisms have yet to be explored.

However, the shortcomings of our descriptive study should be noted. First, the sequencing data and tumour tissue chips are based on a variety of platforms and databases, and systematic errors and bias are inevitable. Second, our study analysed only JAK1 expression and immune cell infiltration using a variety of databases, which still needs to be verified by specific in vitro experiments. Finally, the precise regulatory pathway of JAK1 in the TME of NSCLC still needs to be further explored.

In summary, the elevated expression of JAK1 is associated with superior prognosis and abundant immune cell infiltration in NSCLC. These findings may lay the foundation for immunotherapy for NSCLC.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12859-021-04379-y.

Additional file 1: Table S1. Association between JAK1 expression and prognosis with different clinicopathological features of NSCLC by Kaplan-Meier plotter (specific survival data). Fig. S1. Correlation between JAK1 expression level and immune cell infiltration in LUSC from the TISIDB web portal (501 samples). (A-H) JAK1 expression had no significant correlation with infiltrating levels of Act_CD4 and was significantly positively correlated with infiltrating levels of Act_IDCs, IDCs, neutrophils, NK cells, pDCs, Tcm_CD4 and Tem_CD8. LUSC, lung squamous cell carcinoma; Act_IDCs, activated CD4 T cells; Act_IDCs, activated dendritic cells; IDCs, immature dendritic cells; NK cells, natural killer cells; pDCs, plasmacytoid dendritic cells; Tcm_CD4, central memory CD4 cells; Tem_CD8, effector memory CD8 cells. A P value less than 0.05 indicated statistical significance.

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Authors’ contributions
KS and YW wrote the main manuscript text. WL, TL and YS mainly involved in the design of articles and financial support. XJ, ZL, PZ, XW, and MF help with the making of charts and diagrams for the article. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this article.

Declarations

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Not applicable.

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The authors declare no competing financial interests.

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