ADRB2 Expression Predicts the Clinical Outcomes and is Associated with Immune Cells Infiltration in Lung Adenocarcinoma

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Research Article

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Abstract
The gene encoding beta2-adrenergic receptor (β2-AR), adrenoceptor beta 2 (ADRB2), has been reported to closely associated with various cancers. However, its role in lung adenocarcinoma (LUAD) remains controversial. This research shed light on the prognostic value of ADRB2 in LUAD and further explored its association with immune cell infiltration. ADRB2 was significantly decreased in LUAD. ADRB2 expression in LUAD was significantly correlated with gender, smoking status, T classification, lymph node metastasis, and pathologic stage. Patients in the low ADRB2 expression group presented with significantly poorer overall survival (OS) and disease-specific survival (DSS). Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Set Enrichment Analysis (GSEA) results showed that ADRB2 participates in immune response. The expression of ADRB2 was positively correlated with the infiltration level of most immune cells. Notably, ADRB2 is involved in LUAD progression partly by regulating the immune microenvironment, which may potentially serve as a significant prognostic biomarker as well as a potential drug target.

Introduction
Lung cancer is the primary cause of malignant tumor mortality globally. LUAD, one of the highest mortality rates and most aggressive forms of cancer, with a low 5-year survival rate <5%. Late diagnosis may lead to difficulties in the treatment and prediction of prognosis. Thus, an in-depth study of the molecular mechanisms underlying LUAD progression is urgently needed. At present, there remains an unmet clinical need for tumor biomarkers, and the search for these could lead to more effective treatments and longer survival.

G-protein-coupled receptors (GPCRs) consist of a large family of integral membrane proteins with seven transmembrane helices. Adrenergic receptors (ARs), a member of GPCRs, are classically divided into two main groups: α-and β-adrenoceptors (β-AR, which is divided into β1, β2, and β3 subtypes). β-AR could facilitate cell proliferation, migration, invasion, inflammation, angiogenesis, apoptosis, cell immune response, and epithelial-mesenchymal transition by regulating multiple cancer-related cellular processes. Dysregulated expression of β2-AR was observed in various cancers, including breast cancer, hepatocellular carcinoma, prostate cancer, and ovarian carcinoma. Moreover, abundant β2-AR expression was found to be closely linked with poor clinicopathological characteristics, tumor recurrence, metastasis, and poor prognosis. Although β2-AR is a carcinogenic biomarker; however, the clinical significance of its expression in patients with LUAD has not been thoroughly elucidated yet.

It is well known that the tumorigenesis, progression, OS, prognosis, and relapse of tumors are strongly linked to the expression of tumor genes. The gene encoding β2-AR, ADRB2, maps to human chromosome 5q31–q32 and is composed of a single exon of 2015 nucleotides. The effect of ADRB2 on lung cancer remains controversial. Mei et al. identified ADRB2 polymorphisms that were correlated with increased lung cancer risk. Nevertheless, Zheng et al. found that ADRB2 was underexpressed in LUAD tissues and low ADRB2 expression is associated with poor clinical outcomes. The other research by Wang et al. reached the same conclusion.

Based on The Cancer Genome Atlas (TCGA) dataset, LUAD dataset was acquired for bioinformatics analysis to verify that ADRB2 expression was significantly down-regulated in LUAD. Next, the relationship between ADRB2 gene expression and clinical traits was further investigated. The expression of ADRB2 was highly correlated with immune infiltration, which further confirmed that ADRB2 could be used as a prognostic biomarker of LUAD.

Results

Patient characteristics

Patient characteristics are summarized in Table 1, including sex, age, smoking status, TNM stage, and pathologic stage.
### Table 1
Demographic information of patients with lung LUAD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td></td>
<td>535</td>
</tr>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Female</td>
<td>286 (53.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>249 (46.5%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;=65</td>
<td>255 (49.4%)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>261 (50.6%)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>75 (14.4%)</td>
</tr>
<tr>
<td>Yes</td>
<td>446 (85.6%)</td>
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<tr>
<td>T stage</td>
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</tr>
<tr>
<td>T1</td>
<td>175 (32.9%)</td>
</tr>
<tr>
<td>T2</td>
<td>289 (54.3%)</td>
</tr>
<tr>
<td>T3</td>
<td>49 (9.2%)</td>
</tr>
<tr>
<td>T4</td>
<td>19 (3.6%)</td>
</tr>
<tr>
<td>N stage</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>348 (67.1%)</td>
</tr>
<tr>
<td>N1</td>
<td>95 (18.3%)</td>
</tr>
<tr>
<td>N2</td>
<td>74 (14.3%)</td>
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<td>2 (0.4%)</td>
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<tr>
<td>M stage</td>
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<tr>
<td>M0</td>
<td>361 (93.5%)</td>
</tr>
<tr>
<td>M1</td>
<td>25 (6.5%)</td>
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<tr>
<td>Pathologic stage</td>
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<tr>
<td>Stage I</td>
<td>294 (55.8%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>123 (23.3%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>84 (15.9%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>26 (4.9%)</td>
</tr>
</tbody>
</table>

**ADRB2 Expression Level in LUAD**

Based on the TCGA database, ADRB2 mRNA expression level was analyzed in 594 tissues. Box plots showed ADRB2 mRNA expression levels in 59 adjacent non-tumor tissues and 535 LUAD tissues. As shown in Figure 1A, ADRB2 was down-expression in LUAD tissues compared with those in normal tissues (P<0.001, Figure 1A). Moreover, ADRB2 was significantly lower in males (P<0.001, Figure 1C) and in patients with a smoking history (P<0.001, Figure 1D).

**Association between ADRB2 and TNM Stages in LUAD Patients**

To better understand the impact of ADRB2 on LUAD patient prognosis, Kruskal–Wallis analysis was performed to determine the relationship between ADRB2 expression and clinicopathological characteristics (pathologic and TNM stages). ADRB2 expression was significantly decreased in LUAD patients (Figure 2A-D). It is noteworthy that ADRB2 expression was inversely correlated with T stage (Figure 2B).

**Relationship between ADRB2 and Clinical Characteristics**

To further investigate the mechanism of ADRB2 in LUAD, the associations between ADRB2 expression and clinical characteristics were investigated. Based on the clinical data of 535 patients with LUAD, logistic regression analysis indicated that the expression level of ADRB2 in LUAD was negatively correlated with gender (OR=0.502 for males vs. females, P<0.001); smoking status (OR=0.489 for yes vs. no, P=0.006); T classification (OR=0.603 for T2 vs. T1, P=0.009; OR=0.346 for T3 vs. T1, P=0.002; OR=0.232 for T4 vs. T1, P=0.007); lymph node metastasis (OR=0.648 for positive vs. negative, P=0.021); and pathologic stage (OR=0.513 for stage III vs. stage I, P=0.008, Figure 3).

**Impact of ADRB2 on the Prognosis of LUAD**

Survival curves were derived to assess the prognosis of high and low-ADRB2 expression in LUAD patients. As displayed in Figure 3, patients in the low ADRB2 expression group presented with significantly poorer OS (P=0.001, Figure 4A) and DSS (P=0.005, Figure 4B) than those in the high ADRB2 expression group. However, PFI did not differ between the two groups (P=0.679, Figure 4C).
Effect of ADRB2 Expression on Survival Based on Univariate and Multivariate analyses

Univariate analysis revealed that pathological stage (HR, 2.664; 95% CI, 1.960-3.621; P<0.001); T stage (HR, 2.317; 95% CI, 1.591-3.375; P<0.001); N stage (HR, 2.601; 95% CI, 1.944-3.480; P<0.001); M stage (HR, 2.136; 95% CI, 1.248-3.653; P=0.006); and ADRB2 expression (HR, 0.612; 95% CI, 0.456-0.821; P=0.095) were meaningful indicators of survival (Table 2). However, ADRB2 expression was not an independent prognostic factor in patients with LUAD at multivariable analysis (HR, 0.703; 95% CI, 0.504-1.056; P=0.095, Table 2).

### Table 2

<table>
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<th>Parameter</th>
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<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>Age</td>
<td>1.223</td>
<td>0.916-1.635</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.894</td>
<td>0.592-1.348</td>
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<tr>
<td>Gender</td>
<td>1.070</td>
<td>0.803-1.426</td>
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<tr>
<td>Pathological stage</td>
<td>2.664</td>
<td>1.960-3.621</td>
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<tr>
<td>T stage</td>
<td>2.317</td>
<td>1.591-3.375</td>
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<tr>
<td>N stage</td>
<td>2.601</td>
<td>1.944-3.480</td>
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<tr>
<td>M stage</td>
<td>2.136</td>
<td>1.248-3.653</td>
</tr>
<tr>
<td>ADRB2</td>
<td>0.612</td>
<td>0.456-0.821</td>
</tr>
</tbody>
</table>

Evaluation of the Diagnostic Capacity of ADRB2 in LUAD

To explore the diagnostic value of ADRB2 for LUAD, receiver operating characteristic (ROC) curve analysis was performed. The results of the ROC curves indicated that ADRB2 was highly sensitive to the diagnosis of LUAD (AUC, 0.994; 95% CI: 0.989-0.999, Figure 5A). Additionally, the AUC was 0.598 for OS, which indicated that the prognostic model had good performance in predicting survival prognosis of patients with LUAD (95% CI: 0.548-0.648, Figure 5B).

Relationship of ADRB2 Expression Level with Immune Infiltration in LUAD

Pearson’s analysis demonstrated that the infiltration of 19 types of immune cells was markedly related to ADRB2 expression, which had a significantly positive relationship with activated DCs (aDCs) and a strongly-positive association with B cells, cytotoxic cells, dendritic cells (DCs), eosinophils, immature DCs (iDCs), macrophages, mast cells, neutrophils, natural killer (NK) cells, neutrophils, plasmacytoid DCs (pDCs), T cells, T helper cells, Tcm T central memory (Tcm), T effector memory (Tem), T follicular helper (TFH), type 1 Th cells (Th1), and type 17 Th cells (Th17) (P<0.001, Figure 6). However, T gamma delta (Tgd) and type 2 Th cells (Th2) (P<0.001, Figure 6) showed a negative association with ADRB2.

ADRB2 Associated Gene Set Enrichment in LUAD

To determine ADRB2-related signaling pathways, GSEA was performed between the high- and low-ADRB2 groups. Significance was assessed using a normalized enrichment score (NES)≥1.5, P≤0.05, and false discovery rate (FDR)≤0.25. KEGG pathway enrichment analysis indicated that 13 important signaling pathways were significantly enriched in the highly expressed ADRB2 phenotypes, including the JAK STAT signaling pathways, leukocyte trans-endothelial migration, chemokine signaling pathway, autoimmune, thyroid disease, Fc epsilon ri signaling pathway, intestinal immune network for iga production, cytokine receptor interaction, B cell receptor signaling pathway, NK cell-mediated cytotoxicity, allograft rejection, Mapk signaling pathway, T cell receptor signaling pathway, and NSCLC. Meanwhile, there were 13 eligible signaling pathways enriched in the low-ADRB2 expression, including spliceosome, RNA polymerase, RNA degradation, citrate cycle (or TCA cycle), cell cycle, pentose phosphate pathway, basal transcription factors, oxidative phosphorylation, DNA replication, mismatch repair, cysteine and methionine metabolism, ubiquitin-mediated-proteolysis, and amino sugar and nucleotide sugar metabolism (Table 3, Figure 7). These results contribute to further exploration of ADRB2 pathophysiological mechanisms.
### Discussion

LUAD is a type of malignant lung tumor that originates from the bronchial mucosal glandular epithelium. Early diagnosis is difficult in most patients. LUAD is characterized by inconspicuous early symptoms, and LUAD is a lung tumor with a significant rate of malignant recurrence, metastasis, and unsatisfactory prognosis. Currently, targeted therapy, chemotherapy, immunotherapy, radiation therapy, and surgery remain the mainstays of therapy for LUAD, but the limitations of these therapies necessitate the development of effective approaches. Despite the remarkable importance of LUAD, a disease that affects millions of people worldwide, its exact pathogenesis is not fully characterized, and many aspects of the disease remain controversial.

ADRB2 is ubiquitously expressed in multiple tissues, including the smooth muscle of the human bronchi, cardiovascular system, central nervous system, and gastrointestinal tract. It has been proposed that gene expression, receptor function, and ligand response could be potentially affected by genetic polymorphisms. In recent years, polymorphisms in ADRB2 gene at different loci have been studied in various diseases, and increasing evidence shows that ADRB2 has a vital place in the occurrence and development of diverse range of cancers. Zhang et al. found that the mRNA expressions of ADRB2 were higher in gastric cancers compared with normal tissues. Moreover, patients with gastric cancer with positive ADRB2 expression exhibited larger tumor size, late clinical stage, lower differentiation, and distant metastasis. In addition, high ADRB2 expression can promote the angiogenic switch in prostate cancer.

<table>
<thead>
<tr>
<th>Low expression</th>
<th>High expression</th>
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<td>Gene set name</td>
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<tr>
<td>KEGG_SPLICEOSOME</td>
<td>-2.229</td>
</tr>
<tr>
<td>KEGG_RNA_POLYMERASE</td>
<td>-2.199</td>
</tr>
<tr>
<td>KEGG_RNA_DEGRADATION</td>
<td>-2.183</td>
</tr>
<tr>
<td>KEGG_CITRATE_CYCLE_TCA_CYCLE</td>
<td>-2.126</td>
</tr>
<tr>
<td>KEGG_CELL_CYCLE</td>
<td>-2.103</td>
</tr>
<tr>
<td>KEGG_PENTOSE_PHOSPHATE_PATHWAY</td>
<td>-2.075</td>
</tr>
<tr>
<td>KEGG_BASAL_TRANSCRIPTION_FACTORS</td>
<td>-2.025</td>
</tr>
<tr>
<td>KEGG_OXIDATIVE_PHOSPHORYLATION</td>
<td>-1.998</td>
</tr>
<tr>
<td>KEGG_DNA_REPLICATION</td>
<td>-1.981</td>
</tr>
<tr>
<td>KEGG_MISMATCH_REPAIR</td>
<td>-1.896</td>
</tr>
<tr>
<td>KEGG_CYSTEINE_AND_METHIONINE_METABOLISM</td>
<td>-1.798</td>
</tr>
<tr>
<td>KEGG_UBIQUITIN_MEDIATED_PROTEOLYSIS</td>
<td>-1.743</td>
</tr>
<tr>
<td>KEGG_AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM</td>
<td>-1.654</td>
</tr>
</tbody>
</table>
and prevent or delay the dominant role of pro-angiogenic factors, leading to tumor progression. β2-AR is encoded by ADRB2 and can bind specifically to endogenous catecholamines (such as adrenaline and noradrenaline), and promotes the production and release of cyclic adenosine phosphate (cAMP). cAMP can further activate and phosphorylate protein kinase A and C to activate downstream signal transduction pathways and promote the proliferation, migration, and metastasis of lung cancer cells. The positive β2-AR expression can occur in several cancers, including hepatocellular carcinoma, colorectal cancer, melanoma, and gastric cancer, and is often indicative of poor prognosis. Nevertheless, in oral squamous cell carcinoma, patients with higher β2-AR had a significant longer DSS and OS. Yazawa et al. retrospectively analyzed 328 surgically-resected patients with NSCLC and found that positive β2-AR expression was found in 29% of LUAD tissues, which markedly increased compared with non-adenocarcinoma tissues. A high level of β2-AR expression was associated with vascular invasion, tumor cell proliferation, and poor prognosis in patients with LUAD. On the other hand, in the TME, and can be observed at the individual stages of carcinogenesis. B cells can prolong the survival of cancer patients by inhibiting tumor progression and preventing metastasis. In addition, antibodies produced by B cells are essential mediators of tumor cell death. Cytotoxic T lymphocytes (TILs) are major players in antitumor immunity and can lead to apoptosis of cancer cells through a series of steps; therefore, high infiltration of TILs is a favorable prognostic marker for many cancers. DCs are the most effective antigen-presenting cells to induce primary tumor immune response, and in NSCLC patients, an increased DC count was significantly associated with an increase in DSS. The role of macrophages in cancer progression is still controversial. Tumor-associated macrophages (TAMs) are one of the main M1 type. Mast cells, which have cytokotic effects on cancer cells, can enhance the immunity of patients with LUAD against cancer cells and improve their postoperative prognosis. NK cells are cytotoxic and it is essential in the immune monitoring of cancers. Carrega et al. found that in resected LUAD tissues, increasing numbers of infiltrating NK cells were associated with favorable patient survival outcomes. T cells are the most abundant monocytes infiltrating the NSCLCs. T cells can secrete cytokines to inhibit tumor stroma formation and use cytokotic molecules to kill epithelial nuclear stromal cells. Al-Shibli et al. reported that T cell infiltration is associated with better DSS, and T cells are an independent indicator of survival. T helper cells play an important role in cancer immunity by secreting cytokines. Both Th1 and Th17 cells produce proinflammatory factors, and their extensive infiltration can significantly improve clinical outcomes in a variety of cancers. Large infiltration of cytotoxic T cells in tumor tissues is associated with longer survival. Studies have shown that TFH has an antitumor response, and IL-21 secreted by TFH induces the activation, proliferation, and differentiation of B cells. ADRB2 expression may up-regulate the levels of infiltrating immune cells to limit the development of LUAD. In contrast, ADRB2 was negatively correlated with Th2 cells and Tgd. Th2 cells have many pro-neoplastic activities and take part in cancer progression by cytokine release. Th2 cells are dominant in lymphocytes from malignant pleural effusion in patients with lung cancer. Current studies have revealed that Tgd has a pro-tumor effect, which can inhibit innate and adaptive immunity by inducing immunosenescence. To summarize, low ADRB2 expression is associated with poor prognosis of LUAD. These results show that ADRB2 expression level affects the immunity activity in the TME, and ADRB2 might be a valuable biomarker for the immune status in LUAD patients.

To further explore the mechanism of ADRB2 in LUAD, the signaling pathways involved in ADRB2 were screened. In the ADRB2 high-expression group, ADRB2 associated genes were significantly enriched in immune signaling pathways (such as B cell receptor signaling pathway, T cell receptor signaling pathway, and NSCLC, NK-cell-mediated cytotoxicity, chemokine signaling pathway, and Jak STAT signaling pathway), in KEGG analysis. Those are significant in the tumorigenesis, development, and invasion of malignancies. On the other hand, in the ADRB2 low-expression group, ADRB2 correlated genes were enriched in metabolism-related pathways, including RNA polymerase, citrate cycle, pentose phosphate pathway, oxidative phosphorylation, cysteine and methionine metabolism, and amino sugar and nucleotide sugar metabolism, implying that ADRB2 up-regulated the signaling pathways associated with...
immune response and induced antitumor efficiency. Therefore, ADRB2 expression was down-regulated as LUAD progressed, and the TME switched from an immune-active state to a metabolic state. The ADRB2 expression can be considered a biomarker to predict immune response.

At present, most studies on the relationship between ADRB2 and the occurrence and progression of LUAD are based on its gene expression product, β2-AR, and its signaling pathway. This study revealed ADRB2 as a key gene in the immune microenvironment of LUAD by performing a bioinformatics analysis, to provide evidence for ADRB2 as a potential prognostic marker for LUAD. However, some limitations arise in the research. Firstly, the present research was limited by the small number of cases, and a large cohort is needed to validate the results of this research. Secondly, this research primarily focused on the expression of ADRB2 mRNA from TCGA, and without involving β2-AR levels in LUAD tissues. Thus, this study still needs large-sample, multi-center, multi-ethnic clinical trials and basic experimental studies to prove the prognostic value of ADRB2 in LUAD.

**Conclusion**

In summary, ADRB2 expression was significantly down-regulated in patients with LUAD. ADRB2 is involved in LUAD progression partly by regulating the immune microenvironment, which may potentially serve as a significant prognostic biomarker as well as a potential drug target.

**Materials And Methods**

**TCGA Data**

On or before November 13, 2021, the mRNA profile was extracted from TCGA (https://cancergenome.nih.gov/), including 535 LUAD samples and 59 normal samples. Relevant clinical information was derived from TCGA. The relevant data TCGA provided is open-access, no additional approval from the Ethics Committee were required. All methods were performed in accordance with the relevant guidelines and regulations.

**ADRB2 Expression and Survival Analyses**

The original expression data downloaded from TCGA were processed using the Perl programming language. The differential ADRB2 expression were analyzed by Mann-Whitney U test or Kruskal-Wallis test when appropriate, and the results were visualized using the "limma" and "beeswarm" package of R software. Survival data were extracted and analyzed using the Perl programming language, and patients without complete survival state and time were removed. Subsequently, we matched the complete survival data with ADRB2 expression data and obtained 499 patients’ data. In survival analysis, the ADRB2 mRNA expression level was split into two groups by the median expression value, and OS, DSS, and progression-free interval (PFI) were evaluated with Kaplan-Meier analysis and log-rank test. A Kaplan-Meier survival curve was constructed by the survival package of R software. The diagnostic capacity of ADRB2 was evaluated using ROC curve.

**Univariate and Multivariate Cox Regression Analyses**

Both univariate and multivariate analyses of clinical pathological parameters were performed adopting Cox proportional hazards analysis. In addition, we quantitatively evaluated the independent predictive value of clinicopathological parameters and ADRB2 expression for survival and explored the prognostic effect of ADRB2 on survival after adjusting for other confounding factors. Meanwhile, when matching it with ADRB2 expression data, incomplete clinical information was excluded.

**Evaluation of Immune Infiltration**

First, GSEA method from the R package “GSVA” was used to present infiltration enrichment of 24 common immune cells in each sample, including mast cells, DCs, iDCs, macrophages, eosinophils, TFH, Th1, neutrophils, pDCs, T cells, NK cells, B cells, aDCs, Tem, T helper cells, cytotoxic cells, Tcm, CD8+ T cells, regulatory T cells (Treg), NK CD56 bright cells, Th17, NK CD56dim cells, Tgd, and Th2. After that, Pearson’s analysis was used to investigate the relationship between ADRB2 expression level and 24 immune cell infiltration in LUAD. Wilcoxon rank test was used to compare the levels of immune cell infiltration between different ADRB2 expression groups.

**Gene Set Enrichment Analysis (GSEA)**

All LUAD patients in TCGA dataset were allocated into high and low group based on the expression of ADRB2. GSEA was used as a signaling pathway analysis tool to explore the signaling pathways related to ADRB2 in LUAD. GSEA between high and low ADRB2 expression was performed using GSEA 3.0. Phenotypes were determined based on ADRB2 expression levels. The gene set “c2 all.v6.0 symbols.gmt” was used for the enrichment analysis. KEGG analysis was performed to explore the significant pathways associated with ADRB2 expression.

**Statistical Analysis**

The differential ADRB2 expression was analyzed by Mann-Whitney U test or Kruskal-Wallis test. The correlation between ADRB2 expression and clinicopathological parameters was analyzed using the Chi-square test and logistic regression. Survival curves were analyzed with Kaplan–Meier analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.4, and the level of statistical significance was defined as a P<0.05.

**Declarations**
Data availability

The datasets generated and/or analysed during the current study are available in The Cancer Genome Atlas (TCGA) dataset (https://cancergenome.nih.gov/).

Author contributions

L.Y. J. wrote the original draft, F. X. prepared the figures and tables, J. T. Z. and W. D. Ch. analyzed the raw data, X. Y. and X. B. C. downloaded the raw data from TCGA database, X. L. and M. H. G. reviewed the relevant literature, Q. Q. W. made contribution to the language, Z. T. C. edited the manuscript and made revisions. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests.

References


Figures
Figure 1
The ADRB2 expression and its relationship with clinical characteristics based on TCGA data. (A) Boxplot of ADRB2 expression between the LUAD and normal tissues. The expression of ADRB2 is grouped by age (B), gender (C), and smoking status (D). 

Figure 2
The expression of ADRB2 is grouped by pathological stage (A), T stage (B), T stage (C), and M stage (D). *P<0.05, **P<0.01, ***P<0.001, ns: not significance
<table>
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<th>Total (N)</th>
<th>OR (95% CI)</th>
<th>P value</th>
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<td>Gender</td>
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<td></td>
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<td>Male vs. Female</td>
<td>535</td>
<td>0.502 (0.355–0.707)</td>
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<td>0.489 (0.290–0.809)</td>
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<td>T stage</td>
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</tbody>
</table>

Figure 3
Relationship between ADRB2 and clinical characteristics

A)
Survival analysis of ADRB2 expression in LUAD patients: OS (A), DSS (B), and PFI (C)

Overall Survival
HR = 0.61 (0.46–0.82)  
P = 0.001

Disease Specific Survival
HR = 0.55 (0.40–0.85)  
P = 0.005

Progress Free Interval
HR = 0.95 (0.73–1.23)  
P = 0.679
Figure 5

The ROC curve of ADRB2-associated diagnostic model (A). The ROC curve for predicting OS (B) in LUAD patients

Figure 6

The relationship between immune cell infiltration and ADRB2 expression (A). The infiltration levels of immune cell populations in lung adenocarcinoma (LUAD) patients with different ADRB2 expression (B). *P<0.05, **P<0.01, ***P<0.001

Figure 7

Enrichment plots from gene set enrichment analysis (GSEA)