Identification and validation of immune-related lncRNA prognostic signature for lung cancer

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Abstract

Background: Since lung cancer (LC) has a poor prognosis worldwide, this study focuses on constructing the immune-related lncRNAs (IRlncRNAs) model for improving survivability among lung cancer patients.

Methods: This work identified immune-related differentially expressed genes (IRDEGs) in cancer compared with healthy tissues based on The Cancer Genome Atlas (TCGA)-derived expression profiles. Prognostic genes were later screened by univariate Cox regression, thereafter, multivariate Cox regression was performed to establish a prognostic risk model. After evaluating risk scores of all cases, the risk model was used to perform a clinical correlation analysis.

Results: This work established a 6 immune-related genes (IRGs)-based signature. It suggested the poor survival of high-risk patients, with the area under the receiver operating characteristic (ROC) curve (AUC) value being 0.776. Besides, high-risk IRGs like IPO5P1 and AC090559.1 were associated with significant malignant clinical manifestations. Further, IRlncRNAs were related to cell cycle and DNA damage repair through KEGG enrichment analysis.

Conclusion: Our as-constructed signature might be the model to effectively predict LC survival. Moreover, tumor immunity analysis helped to develop efficient clinical treatments.

Introduction

Lung cancer (LC) accounts for a major factor inducing cancer-associated death globally, which affects 1,898,160 USA people and induces 608,570 deaths in 2021 [1, 2]. Despite the general understanding of the biology of the disease, significant advances in prevention, screening, predictive biomarker application, improvements in treatments, LC cases still have poor survival, with the 5- and 10-year overall survival (OS) being < 15% and < 7%, separately [3]. In addition, there are different factors affecting LC survival. Therefore, it is necessary to screen and detect novel functional genes for understanding disease pathogenesis and developing targeted therapy against lung cancer.

An increasing number of recent articles pay attention to onco-immunology, besides, many immune-checkpoint inhibitors (ICIs) have been identified, which exhibit potent and persistent activities among cancer cases[4], including lung cancer[5]. Therefore, clinicians and investigators have paid great attention to immunotherapy, because it is effective on cancer treatment. In addition, ICIs including PD-1[6], PD-L1[7], GINS4[8], together with cytotoxic T-lymphocyte antigen 4 (CTLA-4)[9] have made remarkable clinical achievements[10]. Hence, abnormal immune-related lncRNAs (IRlncRNAs) levels may predict the prognosis of LC cases, which can be adopted to be candidate therapeutic targets.

In the present study, the immune phenotype was profiled in 496 lung cancer cases with TCGA-derived whole-genome expression profiles, and the IRlncRNAs signature was constructed for LC cases.

Materials And Methods

Collection sample datasets of lung cancer

This work obtained clinical information and LC transcriptome fragments in TCGA-GDC (https://portal.gdc.cancer.gov). Overall, 496 lung cancer samples and 54 precancerous/normal samples were collected in this study. Furthermore, we eliminated cases with unavailable survival information or those with survival ≤ 30 days since the cause of death was infection or hemorrhage and not lung cancer[11, 12]. The clinical information and the complete messenger RNA (mRNA) profile data of the samples are publicly available.

LncRNA profile mining

This work established the lncRNA profiles with the previous description[13]. First of all, this work discovered non-coding or protein-encoding genes, and just preserved long non-coding genes within NetAffx Annotation files. Consequently, the present study acquired 11593 lncRNAs, and later collected immune-related genes (IRGs) based on Molecular Signatures Database v4. 0 [14] (Immune system process M13664, Immune response M19817). We obtained altogether 279 IRGs along with 446 IRlncRNAs by the construction of co-expression IRlncRNAs network ($P \leq 0.001$).

Identification of immune-related lncRNA prognostic signature for lung cancer

This work calculated risk score according to previous description[15, 16] by the following formula,

$$\text{Risk score} = \beta_{gene1} \times expr_{gene1} + \beta_{gene2} \times expr_{gene2} + \cdots + \beta_{genen} \times expr_{genen} \quad (1)$$

Prognostic relations of risk score with age, gender, TNM stage and clinical stage (tumor grade was all unknown, which were not included in the following study) were analyzed by univariate as well as multivariate Cox regression for constructing the signature of prediction survival. Additionally, this work also assigned risk score by linearly combining regression coefficient (β)-weighted lncRNA level. β could be determined based on univariate Cox regression-derived hazard ratio (HR) after log transformation [13]. At last, all cases were classified as high- or low-risk group in subsequent analysis.

Statistical analysis

We ranked 6 most significant IRlncRNAs according to corresponding P-values ($P \leq 0.01$) in ascending order. R software (version 3.2.3) was adopted for principal components analysis (PCA), univariate and multivariate Cox regression. Typically, survival status was utilized in univariate Cox regression, whereas R software (http://cran.r-project.org) was employed for Kaplan–Meier (KM) survival analysis. Meanwhile, functional annotation was conducted by gene set enrichment analysis (GSEA) (http://WWW Broad institute.org/gsea/index.jsp) in high- versus low-risk groups. $P < 0.05$ (two-sided) stood for statistical significance.

Results

Data source and processing

This work identified expression profiles of 11593 lncRNA along with 279 IRGs in 496 LC and 54 healthy tissues. Besides, clinical information from 523 TCGA-derived cases was also collected. Thereafter, 446 IRlncRNAs were obtained from the co-expressed IRGs ($p < 0.001$). Later, correlation coefficients were determined to represent 1854 lncRNAs with positive correlation.

IRlncRNAs identification and prognostic model establishment

Based on the survival dataset of the lung cancer samples, 446 lncRNAs were analyzed by univariate Cox regression for their expression patterns. Upon the threshold of $P < 0.001$, 17 lncRNAs showed differential expression (Fig. 1a). Using multiple Cox regression analyses, this work also discovered three lncRNAs, including AP000695.1, AC079949.1, and ABALON, based on those 6 lncRNAs (Table 1). Later, those 6 lncRNAs levels were determined to measure risk scores of diverse samples. Risk score =— 0.44*AC090559.1—0.41*AC026355.1—0.32*IPO5P1 + 0.46*AP000695.1—0.40* AC025048.4 + 0.50*ABALON (Table 1). According to KM curve analysis on the basis of median risk score, high-risk samples had poor OS compared with low-risk samples, which indicated that risk score was efficient in predicting prognosis ($p = 2.789e - 07$)(Fig. 1b). This work also drew scatter plot and risk curve for demonstrating survival status and risk score in diverse LC samples. As a result, high-risk patients had mortality rate and risk coefficient compared with low-risk ones (Fig. 3c and d). Based on heatmap regarding the expression levels of the above 6 lncRNAs within LC tissues, AP000695.1 showed high expression among high-risk patients, whereas AC090559.1, AC026355.1, IPO5P1, AC025048.4, and ABALON showed high expression within low-risk cases (Fig. 1e). To sum up, the above results discovered 6 IRlncRNAs to be the signatures to predict LC prognosis.

Evaluation of immune-related lncRNAs as independent prognostic factors in patients with lung cancer

This work analyzed clinicopathological variables that independently predicted prognosis, like age, pathological stage and sex, for determining the prognostic significance of those 6 IRlncRNAs within LC. To this end, we conducted univariate as well as multivariate Cox regression. Upon univariate regression, the HR along with 95% CI of risk score was 1.956 and 1.671–2.289 ($p < .001$), while those in multivariate regression were 1.805 and 1.522–2.141 ($p < 0.001$), separately. According to the results, those 6 lncRNAs served as the factors to independently predict prognosis of LC cases (Fig. 2a and b). In addition, this work plotted the time-dependent receiver operating characteristics (ROC) curve for comparing whether risk score was sensitive and specific for predicting LC survival. For risk score, its area under the curve (AUC) was determined to be 0.776 (Fig. 2c), indicating the high reliability of our 6 lncRNA signatures. Based on the above findings, those 6 IRlncRNAs might independently predict LC prognosis.

We also analyzed the relation of one individual lncRNA expression with clinical factors for exploring how those target lncRNAs affected LC. With regard to sex alone, AC090559.1 had a significant ($p < 0.05$)

impact, and the other five lncRNAs were not significant (Fig. 3a). Age came to similar findings (Fig. 3b). As for the different lung cancer stage, IPO5P1 increased with the tumor stage, and others decreased. AC090559.1 was considered to be significant in the T stage (Fig. 3c) and M stage (Fig. 3d), IPO5P1 was considered to be significant in the T stage (Fig. 3e).

Analysis of immune status between low and high-risk groups

This work conducted PCA for analyzing high- and low-risk group distribution based on the IRlncRNA set and genome-wide expression patterns. Consequently, all patients were classified as 2 groups, and high-risk LC cases had markedly different immune status from low-risk patients according to risk gene sets (Figs. 4a). However, PCA carried out according to immune-related LncRNAs (Fig. 4b), immune genes (Fig. 4c), and genome-wide expression profiles (Fig. 4d) revealed a weak distinct immune status separation among diverse groups. Additionally, upon GSEA, IMMUNE_RESPONSE (Fig. 4e) together with IMMUNE_ SYSTEM_PROCESS (Fig. 4f) showed high enrichment level among high-risk patients compared with low-risk counterparts. We adopted the C7 collection sets (IMMUNOLOGIC_SIGNATURE) in GSEA for analyzing DEGs. As a result, there were 279 markedly enriched gene sets (thresholds, NOM $P < 0.05$ and FDR < 0.05). The 6-lncRNA prognostic model was tightly related to immune status in LC cases.

Analysis of immune-related lncRNAs pathways in enrichment between low-risk and high-risk groups

GSEA of high- versus low-risk groups revealed critical pathways according to training set. For high-risk patients, pathways enriched by Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis included cell cycle, base excision repair, and DNA replication signaling pathway. On the other hand, functions enriched among low-risk patients included the primary bile acid biosynthesis within IGA generation intestinal immune network signaling pathway (Fig. 5, Table 2).

Discussion

Lung cancer (LC) represents a frequently occurring cancer globally [17]. Targeted drugs have achieved significant efficacy in treating "oncogenic driver mutations" with in-depth research on tumor pathogenesis and therapeutic strategies in lung cancer. These drugs mainly improve the survival rate of lung cancer patients by targeting the EGFR-TKI mutation. Gefitinib and Erlotinib are the first clinically approved agents to treat LC, which achieve favorable outcomes in PFS relative to chemotherapy[18, 19].

Additionally, applying PD-1/PD-L1 inhibitors ushers in the novel path to treat cancer cases. Such ICIs display persistent clinical activity among advanced cancer cases, and their emergence greatly improves cancer patient prognosis. Therefore, they are introduced in treating some solid tumors, like hepatocellular carcinoma (HCC), triple-negative breast cancer (TNBC), non-small-cell lung cancer (NSCLC), colorectal carcinoma (CRC), and melanoma [20, 21]. Compared with chemotherapy, pembrolizumab (the PD-1 antibody) and atezolizumab (the PD-L1 antibody) are found previously to enhance patient survival [22].

This new therapeutic approach raises the question of identifying treatment-responsive cases. Immunohistochemistry (IHC) has been previously suggested as the predicting factor for treatment responses in patients through the detection of PD-L1 level on cancer cell surface [23, 24]. Unfortunately, since the response rate to therapy is around 20%, not all the patients with abnormal PD-1 and PD-L1 expression respond to treatment and depict improved tumor prognosis. Although most patients with an initial response subsequently progress [25, 26], little is known about PD-1's resistance mechanism within LC. More and more studies have been conducted to analyze genomics with regard to PD-1 response, like elevated tumor mutational burden (TMB), changes in DNA damage response and repair (DDR) genes [27], and the aberrant expression of long non-coding RNAs[28]. Moreover, LIMIT, a previously unknown cancer immunogenic lncRNA, could rescue MHC-I expression through the LIMIT-GBP-HSF1 signaling axis and suggest a promising immunotherapy approach against cancer [29]. Another study identified lncRNA AC007255.1 to be the prognostic IRlncRNA in esophageal cancer (EC)[30].

However, the relationship between immune-related lncRNAs and lung cancer remains unclear. Clinicians and researchers have attempted to explore markers that could identify patients benefiting from immunotherapy. In addition, no creditable biomarkers have been developed clinically. Consequently, this work first analyzed IRGs within LC based on the TCGA-GDC database, retrieved 17 IRlncRNAs, and later established 6 IRlncRNAs expression levels. Subsequently, this work found that 6 IRlncRNAs interacted with other factors as possible independent prognostic factors determined using univariate as well as multivariate regression. Moreover, they were also positively related to tumor clinicopathological features, like age, TNM and sex. The outcomes suggested that these six immune-related lncRNAs could become novel markers of lung cancer prognosis, provide new ideas, and open new research directions for developing therapeutic strategies for tumor patients. According to functional analysis, risk score was associated with DNA repair and cell cycle.

Our study had certain limitations: (1) The TCGA dataset was randomly and equally divided as training and validation sets, and this might lead to possible study bias. (2) There were significant differences in LC, healthy and paraneoplastic samples collected in TCGA database, making it impossible to differentially analyze 6 IRlncRNAs in LC compared with healthy tissues. (3) This work did not validate functional roles of those 6 IRlncRNAs, therefore, more studies should be conducted for further validation. Therefore, the biological functions of these six lncRNAs in lung cancer and their possible molecular mechanisms leading to tumor progression will be investigated through subsequent research.

Conclusion

This work discovered 6 IRlncRNAs to be the possible LC biomarker. At the same time, the signature might be used clinically as a supplement to TNM classification, so as to improve malignancy grade and prognostic outcome prediction of cancer.

Declarations

Conflicts of Interest

None.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

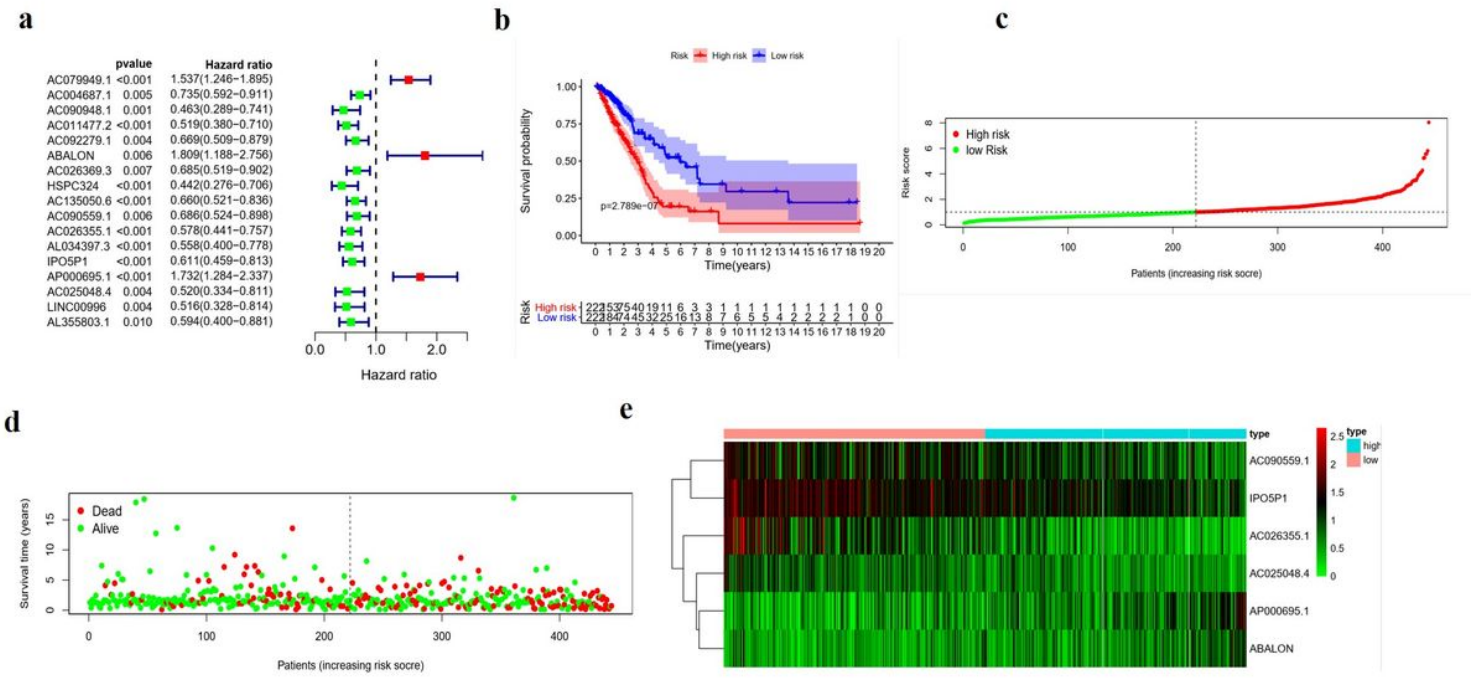

Figure 1

IRlncRNA prognostic signature detection and evaluation within LC. a. P-values and HRs of IRGs upon univariate Cox HR regression (Criterion: p<.001). b. High-risk cases (red) showed poor OS compared with low-risk cases (blue). c. Risk score was used to reorder the risk curve of diverse samples again. d. Scatter plot showing patient survival, where red and green dots indicating death and survival, separately. e. Heatmap showing the signature expression levels within high- and low-risk patients, where blue and pink bars stand for high- and low-risk groups, separately. The green-to-red evolution stood for 0-2.5 gene expression level.

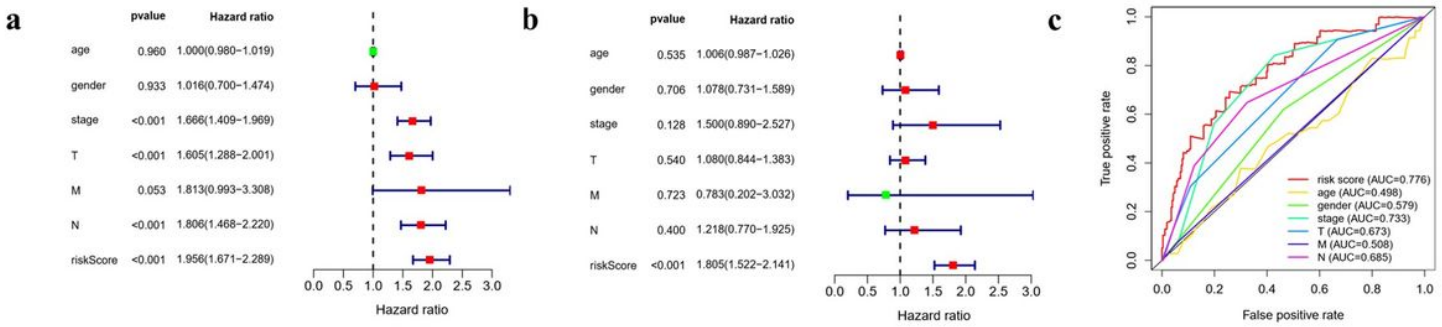

Figure 2

The Cox regression analysis for evaluating the independent prognostic value of the risk score. The univariate (a) and multivariate (b) Cox regression analysis of risk score, age, gender, and TNM stage. (c) The AUC for risk score, age, gender, grade, and TNM stage of the total survival risk score was evaluated based on the ROC curve.

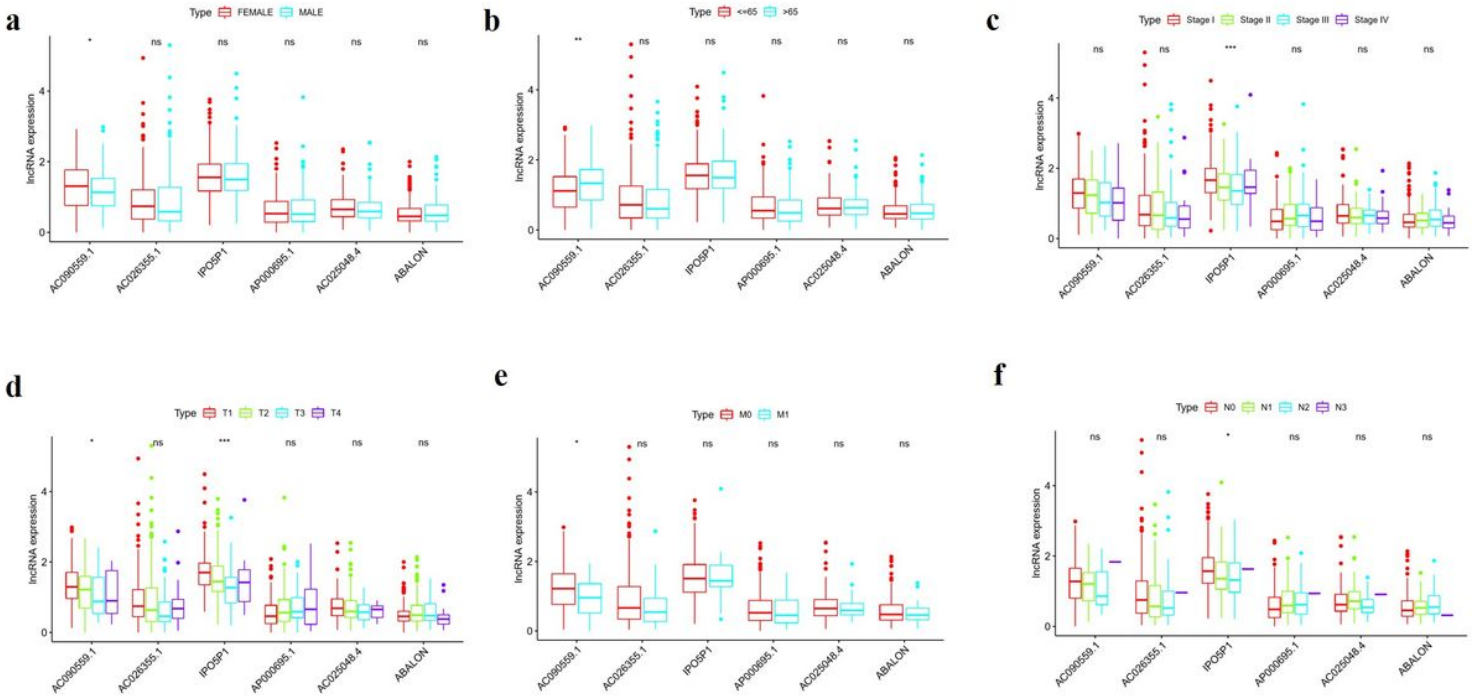

Figure 3

Relations of one individual lncRNA expression with clinical factors. (a–f) stand for age, sex, stage, N stage, T stage, and M stage, separately. *P < 0.05, **P < 0.01, ***P < 0.001. NS, not significant.

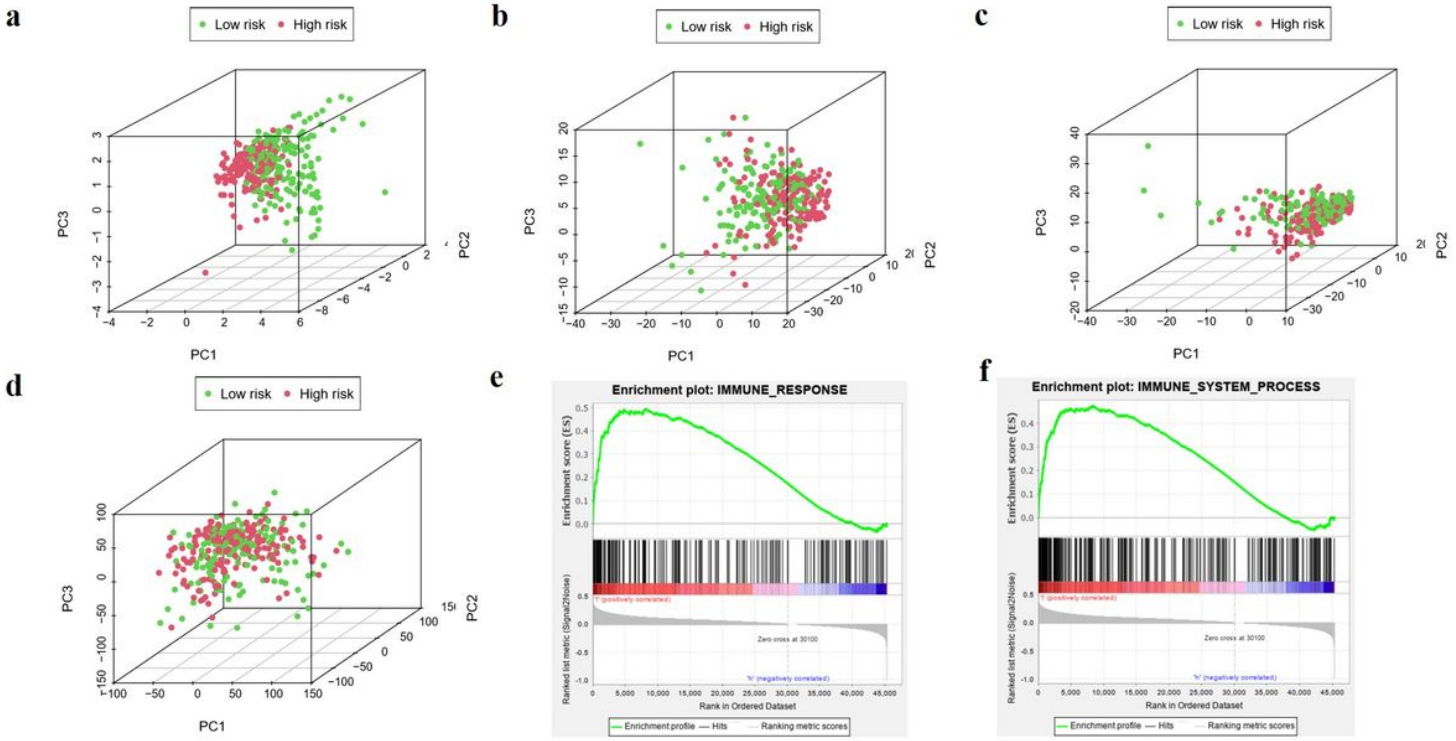

Figure 4

PCA of high- versus low-risk groups according to risk gene sets (4a). PCA of high- versus low-risk groups according to IRlncRNAs, (4b) immune gene, and (4c) entire protein-coding gene lists (4d) GSEA depicting the significantly enriched immune phenotype of high-risk cases (4e and 4f).

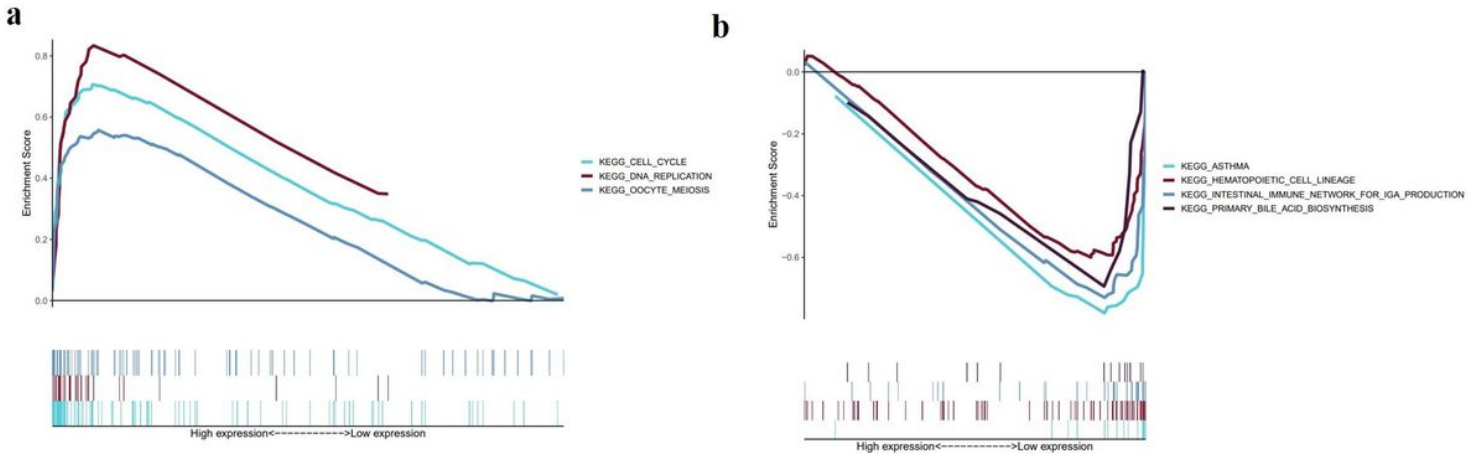

Figure 5

Typical GSEA describing possible KEGG pathways enriched in high- and low-risk groups. (a) High- and (b) low-risk groups.

Supplementary Files

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