Abstract. The current study aimed to identify the potential clinical significance and molecular mechanisms of kinesin (KIF) family member genes in lung adenocarcinoma (LUAD) using genome-wide RNA sequencing (RNA-seq) datasets derived from The Cancer Genome Atlas (TCGA) database. Clinical parameters and RNA-seq data of patients with LUAD from the TCGA database enabled the assessment of the clinical significance of KIF genes, while the potential mechanisms of their interactions in LUAD were investigated by gene set enrichment analysis (GSEA). A gene signature with potential prognostic value was constructed via a stepwise multivariable Cox analysis. In total, 23 KIF genes were identified to be differentially expressed genes (DEGs) between the LUAD tumor and adjacent non-cancerous tissues. Of these, 8 differentially expressed KIF genes were strongly found to be strongly associated with the overall survival of patients with LUAD. Three of these genes were found to be able to be grouped as a potential prognostic gene signature. Patients with higher risk scores calculated using this gene signature were found to have a markedly higher risk of mortality (adjusted P=0.003; adjusted HR, 1.576; 95% CI, 1.166-2.129). Time-dependent receiver operating characteristic analysis indicated that this prognostic signature was able to accurately predict patient prognosis with an area under curve of 0.636, 0.643, 0.665, 0.670 and 0.593 for the 1-, 2-, 3-, 4- and 5-year survival, respectively. This prognostic gene signature was identified as an independent risk factor for LUAD and was able to more accurately predict prognosis in comparison to other known clinical parameters, as shown via comprehensive survival analysis. GSEA enrichment revealed that the KIF14, KIF18B and KIF20A mediated basic cell physiology through the regulation of the cell cycle, DNA replication, and DNA repair biological processes and pathways. On the whole, the findings of this study identified 23 KIF genes that were DEGs between LUAD tumor and adjacent non-cancerous tissues. In total, 8 of these genes had the potential to function as prognostic and diagnostic biomarkers in patients with LUAD.

Introduction

Lung cancer is the primary contributor towards cancer mortality and morbidity in the developed world, including in countries such as China. The latest global cancer statistics report an estimated 2,093,876 new cases and 1,761,007 deaths due to lung cancer worldwide in 2018 (1). These statistics are reflected in China, where there were 733,300 new lung cancer cases and 610,200 deaths due to lung cancer in 2015 (2). Lung cancer presents as either non-small cell (NSCLC) or small cell lung cancer, with the latter further classified into lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). In recent years, an increased number of cases of LUAD has been observed, which has surpassed the incidence of LUSC. LUAD is mostly associated with genetic factors, environmental and other external factors, including smoking. Genetic factors are able to function as more objective biomarkers for the diagnosis, treatment and prognosis of lung cancer.

The kinesin (KIF) family member genes are mainly found in eukaryotic cells, primarily in microtubules. In vitro experiments have demonstrated that the transport of proteins is unidirectional, moving along the negative pole of microtubule towards the positive pole. Therefore, the KIF family genes control mass protein transfer both intracellularly and extracellularly, including functions, such as transporting organelles and material vesicles, and participating in cell mitosis (3-5).
The use of whole-genome sequencing data combined with bioinformatics analysis is an effective method with which to explore prospective molecular mechanisms. The Cancer Genome Atlas (TCGA, https://portal.gdc.cancer.gov) is an open-source project using large-scale genomic sequencing to map the genomes of 33 types of human cancer (6,7), including complete RNA sequencing (RNA-seq) data for LUAD. Numerous studies have reported that KIF family member genes are dysregulated in multiple types of cancer, and can be used as diagnostic and prognostic biomarkers for cancers (5,8-10). In our previous study, we analyzed genome-wide breast cancer RNA-seq dataset from the TCGA database and found that multiple genes belonging to the KIF family could be used as biomarkers for the diagnosis and prognosis of breast cancer (11). Therefore, we concluded that some of the KIF family genes may also be used as diagnostic and prognostic biomarkers of LUAD. In addition, previous studies have also reported that some of the KIF family genes may be used as prognostic indicators of LUAD (12-14).

However, the comprehensive systemic analysis of KIF family genes in LUAD has not yet been reported, at least to the best of our knowledge, and thus the potential underlying molecular mechanism still require further investigation. In order to fill this gap in knowledge, the present study aimed to elucidate the potential molecular mechanisms of KIF family member genes, and to determine their prognostic value in LUAD.

Materials and methods

Data source and pre-processing. Clinical data, as well as the complete RNA sequencing (RNA-seq) library of TCGA LUAD cohort were derived from the TCGA database (https://portal.gdc.cancer.gov/projects/TCGA-LUAD) (6,7,15). Raw RNA-seq was normalized using the R platform of the DESeq package (http://www.bioconductor.org/packages/release/bioc/html/DESeq.html), allowing the identification of the differentially expressed genes (DEGs) of KIF family members between LUAD tumor and adjacent non-cancerous tissues (16). This study does not contain any experiments using human participants or animals performed by any of the authors. Since all datasets included in the current study were downloaded from the TCGA database and data acquisition and application are consistent with the publication guidelines of TCGA, additional approval by an ethics committee is thus not necessary.

Prognostic KIF gene screening. The inclusion criteria and exclusion criteria of the patients with LUAD for survival analysis were as follows: Inclusion criteria: i) LUAD tumor tissues RNA sequencing data set were available; ii) overall survival (OS) time was available and not zero. Exclusion criteria: i) Patient tumor tissues were not subjected RNA sequencing; ii) the OS time was zero or unavailable. Survival analysis was performed using the normalized mRNA gene expression dataset of KIF-related genes and clinical outcome parameters. The subjects were grouped as having either a low or high-expression based on the median expression value of each gene. The prognostic values of KIF family member genes were evaluated via multivariate Cox proportional hazards regression analysis using the R platform of the survival package (https://cran.r-project.org/web/packages/survival/index.html). The group that had a low KIF gene expression was used as the reference group, with all data adjusted for tumor stage. A P-value <0.05 was considered to indicate a statistically significant difference, with the respective gene designated as a prognostic KIF gene.

Construction of a prognostic gene signature based on KIF gene expression. A prognostic gene signature was constructed based on the linear combination of gene expression levels multiplied by a regression coefficient ($\beta$), which was derived from multivariate Cox proportional hazards regression analysis. The prognostic KIF family member genes were inserted into the multivariate Cox regression model using overall survival as the dependent variable. The risk score formula of the prognosis signature was as follows (17-22): Risk score = $\beta_1$ expression of KIF1 + $\beta_2$ expression of KIF2 + $\ldots$ expression of KIFn. Patients were classified as having low or high risks based on the median value of risk scores. A time-dependent receiver operating characteristic (ROC) curve was drawn by the R platform of the survivalROC package (https://cran.r-project.org/web/packages/survivalROC/index.html) in order to evaluate the predictive accuracy of KIF genes expression based prognostic signature for the prognosis of LUAD (23).

Comprehensive survival analysis of mRNA expression-based prognostic signature. The association between LUAD clinical features and the contrasted prognostic signature was investigated using stratified and joint effects survival analysis. A nomogram was generated to evaluate the individualized prognosis risk score based on clinical characteristics and KIF gene expression-based prognostic signature.

Gene set enrichment analysis (GSEA). To further assess the biological pathways that underlie prognostic KIF genes in LUAD OS, GSEA (http://software.broadinstitute.org/gsea/index.jsp) was performed (24,25). GSEA uncovered the potential mechanisms of prognostic-KIF genes using the Molecular Signatures Database (MSigDB, http://software.broadinstitute.org/gsea/msigdb/index.jsp) (26). The results of GSEA that had a false discovery rate (FDR) <0.25, |Normalized Enrichment Score (NES)| >1 and a nominal P-value <0.05 were considered to indicate a statistically significant difference.

Statistical analysis. SPSS version 20.0 software (IBM Corp.) and R3.3.1 (https://www.r-project.org), were used to compute all statistical analyses. The diagnostic receiver operating characteristic (ROC) curves of KIF genes between tumor and adjacent non-cancerous tissues were analyzed and plotted by SPSS version 20.0. The independent samples t-test was used to compare the mRNA expression levels of tumor and adjacent normal tissues. The co-expression correlation between KIF family member genes was assessed by Pearson's correlation coefficient. Survival analyses were assessed using the Kaplan-Meier method and Cox proportional hazard regression model. Clinical parameters with a log-rank test P-value <0.05 in LUAD OS were subjected to further multivariate Cox proportional hazards regression model for adjustment. A value...
of $P<0.05$ was considered to indicate a statistically significant difference.

**Results**

**Study cohort.** A total of 515 patients that contributed 535 tumor tissues and 59 adjacent non-cancerous tissues were extracted from the TCGA database LUAD project. In total, 500 patients with LUAD had complete clinical outcome parameters and RNA-seq data, and these were included into further survival analysis. Univariate survival analysis of the clinical parameters in LUAD OS suggested that tumor stage was significantly associated with LUAD OS (Table I). Expression heatmaps and differential expression fold changes are shown in Figs. 1 and 2, respectively. In total, 25 KIF genes were found to be significantly dysregulated between the LUAD tumor and adjacent non-cancerous tissues, of these, 23 KIF genes were identified as DEGs based on the following criteria: $|\log_2 \text{Fold Change(FC)}| \geq 1$, $P$-value $<0.05$ and FDR $<0.05$. In total, 5 DEGs were found to be downregulated in the LUAD
tumor tissues, whereas the others were upregulated (Table II). Further analysis of the co-expressed KIF genes in the tumor tissues revealed that a majority of KIF genes existed in complex co-expression associations (Fig. 3 and Table SI).

**Tables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n=500)</th>
<th>MST (days)</th>
<th>Crude HR (95% CI)</th>
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<td>264</td>
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<td>1,528</td>
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<td>Stage IV</td>
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<td>Tumor stage**</td>
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<td>826</td>
<td>2.585 (1.894-3.528)</td>
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</tbody>
</table>

*aInformation of age was unavailable for 21 patients; bInformation of tumor stage was unavailable for 8 patients. TCGA, The Cancer Genome Atlas; MST, median survival time; LUAD, lung adenocarcinoma; HR, hazard ratio; CI, confidence interval.

**Figure 3.** Co-expression heatmap of KIF family genes in LUAD tumor tissues. KIF, kinesin; LUAD, lung adenocarcinoma.

**Prognostic KIF gene screening.** Survival analysis of KIF genes in the present study cohort based on multivariate Cox proportional hazards regression model demonstrated a total of 8 KIF genes that were significantly associated with LUAD OS.
The upregulation of these 8 prognostic KIF genes was associated with significantly higher mortality risks in the patients with LUAD. In addition, we also observed that these 8 prognostic KIF genes were notably upregulated.
in the LUAD tumor tissues (Fig. 5A), and ROC curve analysis also substantiated that these 8 prognostic KIF genes may serve as potential diagnostic biomarkers for LUAD (Fig. 5B-I).

**Construction of a prognostic gene signature.** The 8 KIF genes that were significantly associated with LUAD OS on single gene survival analysis were subjected to screening for potential prognostic gene signature combination using the 'step' function. The most significant KIF candidate gene combinations of these 8 KIF genes were further screened for prognostic signature construction. Finally, KIF14, KIF18B and KIF20A were used for the prognostic signature
construction based on the following formula: Expression of $KIF14$ x (0.2437) + expression of $KIF18B$ x (-0.1541) + expression of $KIF20A$ x (0.1926). Survival analysis revealed that patients with high risk scores were more likely to have an increased risk of death (log-rank $P=0.0002$, adjusted $P=0.003$; adjusted HR, 1.576; 95% CI, 1.166-2.129; Fig. 6A and B) and a poorer clinical outcome (median survival time, high risk vs. low risk: 1,081 vs. 1,725 days). The predictive accuracy of this prognostic signature was determined using time-dependent ROC curve analysis, with the results suggesting that the constructed signature was able to accurately predict the 1-, 2-, 3-, 4- and 5-year patient survival, based on the respective area under curves 0.636, 0.643, 0.665, 0.670 and 0.593 (Fig. 6C), respectively. We also noted that the expression levels of the $KIF14$, $KIF18B$ and $KIF20A$ genes exhibited a strongly and positive correlation with each other (Pearson's correlation coefficient $r=0.713$ for $KIF14$ and $KIF18B$; $r=0.760$ for $KIF14$ and $KIF20A$; $r=0.722$ for $KIF20A$ and $KIF18B$; Table S1).

**Stratified and joint effects analysis.** A comprehensive analysis of the nomogram and stratified and joint effects survival analysis was used to further investigate the association between clinical parameters and the prognostic gene signature. Patients that had stage I and stage I+II disease, were of the female sex and were >65 years of age were more likely to succumb to the disease if they also had higher risk scores (Fig. 7A). A nomogram constructed of the risk scores and clinical LUAD parameters demonstrated that the KIF gene expression-based prognostic signature was more accurate compared to other parameters (Fig. 7B).

Joint effects survival analysis between the KIF gene expression-based clinical parameters and prognostic gene signatures indicated that the constructed signature was able to accurately predict the OS of patients with LUAD, particularly when combined with clinical parameters (Fig. 8 and Table III).

**GSEA.** Additional exploration of the biological pathways of the selected KIF genes in relation to LUAD was carried out using a single gene GSEA. An enrichment of c5 suggested that a high expression of $KIF14$ was involved in DNA repair, DNA replication, cell cycle, tumor protein p53 (TP53) binding and mitotic sister chromatid separation biological processes (Fig. 9 and Table SII). Whereas, an enrichment of c2 indicated that a high expression of $KIF14$ influenced the cell cycle, DNA replication, lung cancer poor survival, metastasis, base excision repair, the PLK1 pathway, nuclear factor-$\kappa$B (NF-$\kappa$B) and the TP53 pathway (Fig. 10 and Table SIII). c5 enrichment suggested that a high expression of $KIF18B$ was also involved in cell division, the cell cycle, DNA replication and DNA repair (Fig. 11 and Table SIV), whereas c2 enrichment suggested that high expression of $KIF18B$ was involved in cell division, DNA replication, lung cancer poor survival, metastasis, base excision repair, the PLK1 pathway, NF-$\kappa$B and TP53 pathway (Fig. 12 and Table SV). Similar results were also found for $KIF20A$, where c5 enrichment suggested that a high expression of $KIF20A$ was involved in cell division, cell cycle, DNA replication, DNA repair and the NF-$\kappa$B pathway (Fig. 13 and Table SVI), whereas c2 enrichment suggested that a high expression of $KIF20A$ was involved in cell cycle, DNA replication, lung cancer poor survival, apoptosis, metastasis, DNA repair, the PLK1 and TP53 pathway (Fig. 14 and Table SVII). It is evident that the potential mechanisms of $KIF14$, $KIF18B$ and $KIF20A$ are likely mediated through their influence on cell cycle regulation, DNA replication and
Figure 7. Stratified analysis and nomogram for the risk score and clinical features. (A) Stratified analysis of the risk score in LUAD OS. (B) Nomogram for predicting the 1-, 3-, and 5-year OS using the risk scores and clinical features in LUAD. LUAD, lung adenocarcinoma; OS, overall survival.

Figure 8. Joint effects analysis of risk score and clinical features in patients with LUAD. Joint effects analysis of risk score stratified by the following clinical features in patients with LUAD: (A) Age: Group 1 is low risk and age ≤65 combination, group 2 is low risk and age >65 combination, group 3 is high risk and age ≤65 combination, and group 4 is high risk and age >65 combination. (B) Sex: Group I is low risk and female combination, group II is low risk and male combination, group III is high risk and female combination, and group IV is high risk and male combination. (C) Tumor stage: Group A is low risk and stage I combination, group B is low risk and stage II combination, group C is low risk and stage III combination, group D is low risk and stage IV combination, group E is high risk and stage I combination, group F is high risk and stage II combination, group G is high risk and stage III combination, and group H is high risk and stage IV combination. (D) Tumor stage stratified by early stage and advanced stage: Group a is low risk and stage I+II combination, group b is low risk and stage III+IV combination, group c is high risk and stage I+II combination, and group d is high risk and stage III+IV combination. LUAD, lung adenocarcinoma.
Furthermore, all the c2 enrichment analyses of KIF14, KIF18B and KIF20A were enriched in the gene set of SHEDDEN_LUNG_CANCER_POOR_SURVIVAL_A6, which indicated that the upregulated expression levels of the molecules KIF14, KIF18B, and KIF20A. These findings suggest that these molecules may play crucial roles in DNA repair processes.
genes of this gene set in patients with lung cancer were predictors of a poor survival outcome.

Discussion

KIF family member genes encoded proteins are required for numerous processes, including intracellular transport, chromosome segregation, mitotic spindle formation and cytokinesis, and multiple family member genes have been reported to be dysregulated in various types of cancer (5,8,12,27-29). The prognostic and diagnostic capabilities of KIF family member genes have been demonstrated in various types of cancer. In a previous study, immunohistochemical staining suggested that KIF3A expression was significantly higher in breast cancer (bC) tumor tissues than healthy adjacent tissues (8). Previous studies have demonstrated that an increased KIF2A expression is a predictor of an unfavorable clinical outcome in patients with LUAD and diffuse large b cell lymphoma (12,30). An increased KIF4A expression has also been shown to be strongly associated with a poorer prognosis of patients with BC (9), prostate cancer (PCa) (10) and hepatocellular carcinoma (HCC) (31,32). Similar prognostic values of KIF11 in oral cancer (33) and BC (34) have also been reported. Other members of the KIF gene family have also exhibited similar prognostic values in other types of cancer, such as KIF26B in ovarian cancer (OC) (35) and KIF20B in HCC (36). In the present study, we observed that 26 KIF family member genes were differentially expressed in LUAD and healthy adjacent tissues and identified as DEGs, with 5 DEGs were downregulated and 18 DEGs were upregulated. In total, 8 of these DEGs were identified as diagnostic and prognostic genes for LUAD, which was consistent with the findings of the above-mentioned studies. Three of these genes were used to construct a potential prognostic signature for LUAD.

For 3 KIF genes of the prognostic signature that were identified in the present study, previous studies have observed that KIF14 is notably upregulated in tumor tissues of OC (37,38), pancreatic carcinoma (39), cervical cancer (40), BC (41), PCa (28), glioma (42) and gastric cancer (GC) (43). The function of KIF14 may serve as an oncogene in cancers.
and inhibiting KIF14 has been shown to inhibit the growth of PCa and LUAD cell lines (13,28), to suppress the proliferation of medulloblastoma and NSCLC (44,45), to decrease cancer cell migration and induce apoptosis in HCC (46), as well as to
inhibit tumor metastasis in GC (43), PCa (28) and LUAD (13). In the present study, our results of KIF14 in LUAD were also consistent with those of these previous studies. Our results suggest that KIF14 may be adopted as diagnostic and prog-
nostic indicator for LUAD. Similar with the KIF14, we also identified that KIF18B was upregulated in LUAD tumor tissues, suggesting its utility as a diagnostic and prognostic biomarker in patients with LUAD. Wu et al demonstrated that KIF18B
expression was increased in cervical cancer tumor tissues with an advanced tumor grade and stage. This gene may also function as a cervical cancer oncogene, as the downregulation of \textit{KIF18B} has been shown to inhibit cervical cancer migration.
invasion and cell in vitro (47). Itzel et al identified KIF18B as a novel oncogene that drives carcinogenesis in HCC (48). Our results were very consistent with the results of these previous studies. To the best of our knowledge, this study was the first
to suggest that KIF18B may serve as potential diagnostic and prognostic indicator for LUAD.

Another of our candidate prognostic signature gene, KIF20A, has also been reported to be strongly expressed in nasopharyngeal carcinoma (NPC) (49), NSCLC (14,50,51), HCC (52), cervical cancer (53), glioma (54), OC (55) and clear cell renal cell carcinoma (ccRCC) (56). Furthermore, a high expression of KIF20A in these types of cancers has also been shown to be associated with an increased risk of an unfavorable prognosis (14,49-53,55,56). In addition, previous studies have also demonstrated that a high KIF20A expression is associated with a poor clinical outcome in patients with melanoma (57) and ovarian clear cell carcinoma cells (58). Previous studies have also observed that KIF20A is significantly related to tumor progression, and advanced stage tumor tissues exhibit an increased KIF20A expression level (55,56).

Functional experiment assessment in cancers infers that KIF20A may play a carcinogenic role in cancer, and cancer cell proliferation can be regulated by the overexpression or inhibition of KIF20A (14,52,54,55,58).

In the present study, we also identified the prospective molecular mechanisms using GSEA. KIF family genes play critical roles in chromosome segregation, mitotic spindle formation and cytokinesis. GSEA analysis further verified that KIF14, KIF18B and KIF20A were significant participants in cell cycle regulation, thereby influencing the clinical outcome of patients with LUAD. Previous studies have demonstrated that KIF14 functions to regulate cell apoptosis and proliferation, cytokinesis and cell division (46,59,60). Xu et al demonstrated that inhibiting KIF14 in HCC cell lines can influence the cell cycle and cytokinesis biological process (29). The overexpression of KIF14 in colorectal cancer (CRC) has been shown to promote cell proliferation and accelerate cell cycle progression (61). A similar oncogenic function of KIF20A in the cell cycle and proliferation has also been reported in pan-cancers (14,55,58,62). Itzel et al observed that the overexpression of KIF18B increased the proliferation of HCC cells (48). Based on literature reviewing and prospective molecular mechanism analysis from the current study, it can be concluded that the one of the molecular mechanisms of KIF family genes is the involvement in the prognosis of LUAD mainly by affecting cell cycle-related biological processes and pathways.

Among one of the limitations of this study is that clinical information derived from TCGA was not comprehensive, barring a complete assessment of risk profiles. The results of the current study were also based on a single cohort and lack additional validation cohorts, with verification in larger sample sizes across differing cohorts needed to further verify the findings. Furthermore, the results of this study were derived from RNA sequencing data from the TCGA LUAD cohort and were not validated in additional cohorts by RT-PCR and immunohistochemistry in both the mRNA and protein level. Nevertheless, the resultant 3 KIF gene-signature developed in this study was proven to be a more accurate prognosticator in contrast to other clinical data. These results lay the foundation for further studies into the mechanistic functions of KIF genes as regards the prognosis of patients with LUAD, allowing for further development targeted LUAD therapy.

In conclusion, in this study, using an integrated assessment of KIF family member genes RNA-seq dataset and clinical data of LUAD derived from the TCGA database, we systematically evaluated the differential expression and prognostic values of KIF family member genes, and found that 23 KIF genes were DEGs between LUAD tumor and adjacent normal tissues. In total, 8 of these were found to be potential prognostic and diagnostic biomarkers in patients with LUAD. In addition, we also developed a novel 3 KIF gene-expression-based signature, including KIF14, KIF18B and KIF20A, which may aid in the prognosis of patients with LUAD.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request. All raw data of LUAD, which were included in the current study, can be downloaded from TCGA (https://portal.gdc.cancer.gov/).

Authors’ contributions

LZ and PW designed this study; LZ, GZ, XW, XL, RH, CH, PH, JZ and PW conducted and further performed the study, processed and analyzed the data, as well as interpret the results. LZ wrote this manuscript, and PW guided the writing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The current study does not contain any studies with human participants or animals performed by any of the authors. Since all LUAD datasets included in this manuscript were obtained from The Cancer Genome Atlas, therefore, additional approval by an Ethics Committee was not necessary. In addition, the procedures of this manuscript were in accordance with the Helsinki declaration of 1964 and its later amendments.

Patient consent for publication

Not applicable.
Competing interests

The authors declare that they have no competing interests.

References


