Distinct Diagnostic and Prognostic Values of Kinesin Family Member Genes Expression in Patients with Breast Cancer

Background: This study investigated the diagnostic and prognostic values of kinesin superfamily proteins (KIFs) in breast cancer (BC) patients.

Material/Methods: All data were obtained from the Cancer Genome Atlas. DESeq was run to test for differentially expressed KIF genes. Patients were divided into high- and low-expression groups according to the median expression values of each KIF genes. Survival data were calculated using the Cox proportional hazard model. Comprehensive survival analysis was performed to evaluate the prognostic value of the prognostic signature. Gene set enrichment analysis (GSEA) was conducted to identify associated gene ontology and KEGG pathways.

Results: Bioinformatics analysis showed that all KIF genes were significantly enriched during DNA replication and the cell cycle, and co-expressed with each other. Thirteen KIF genes were differentially expressed in cancer and adjacent tissues, and high levels of KIF15, KIF20A, KIF23, KIF2C and KIF4A genes were significantly correlated with poor overall survival (OS). GSEA showed that BC patients with high expression of KIF15, KIF20A, KIF23, KIF2C and KIF4A were enriched in the cell cycle process, P53 regulation pathway and mismatch repair. Combinations of low expression of KIF15, KIF20A, KIF23, KIF2C and KIF4A were more highly correlated with favorable OS. Nomograms showed that the KIF4A risk score provided the maximum number of risk points (range 0–100), whereas other genes made a lower contribution.

Conclusions: We conclude that 13 KIF genes are differentially expressed in BC tumor tissues, and KIF15, KIF20A, KIF23, KIF2C and KIF4A are associated with prognostic factors in BC.

MeSH Keywords: Breast Neoplasms • Diagnosis • Kinesin • Prognosis • RNA

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Background

Breast cancer (BC) remains the highest occurring cancer in women, in addition to being the third most frequent malignancy globally. In 2012, around 1.7 million persons worldwide had BC and nearly 500,000 died from the disease [1-4]. One among eight or 10 women will develop BC in their lifetime. BC mortality has decreased in North America as well as the European Union, but is still increasing in South America, Africa, and Asia. BC is the most common cause of cancer mortality in developing countries, compared with lung cancer in developed countries [5-7]. Genetic aspects and environmental exposure play a significant part in the etiology of BC [8,9]. The Human Genome Project has led to increasing attention being paid to cancer genetic susceptibility. A genetic factor which dysfunction amid normal tissues and tumors in the genome are the major potential sources of prognostic and diagnostic biomarkers [10]. Also, genes whose expression is interlinked with survival of BC might be prognostic biomarkers, as well as therapeutic targets [11-14]. As in other malignant neoplastic diseases, BC is considered to have dysfunction of numerous gene signaling pathways as well as networks that have an impact on tissue homeostasis.

Material and Methods

Bioinformatics analysis of KIF genes

For analysis of the biological pathways and significance of the KIF family genes, a set of functional enrichment analysis for the KIF family was performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID 6.8, https://david.ncifcrf.gov/home.jsp, accessed August 3, 2018). Enriched P values <0.05 were statistically significant. Gene–gene interactions of KIF family genes were investigated via GeneMANIA (http://www.genemania.org/, accessed August 9, 2018) [22].

Protein–protein interactions were examined by the Search Instrument for the Retrieval of Interacting Genes/Proteins (STRING, https://string-db.org/, accessed August 9, 2018) [23]. We also applied the Cytoscape (version 3.6.1) Biological Networks Gene Ontology (BINGO) instrument for performing Gene Ontology (GO) evaluation on the KIF gene family [24].

Data source

The knowledge of the clinical of BC patients and RNA sequence based on the patients were gathered by the Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/, accessed June 7, 2018). Using the edgeR package in R, we normalized mRNA sequencing data and examined mRNA expression in normal tissues and BC. Genes with an accustomed P value <0.01 and |log, fold-change (FC)| >2 were considered to be significantly different in BC and adjacent tissues. We regarded the genes as being differentially expressed mRNA (DEM). Clinical characteristics of patients with BC included gender, ethnicity (Asian, black, white or other), age at diagnosis (<65 or ≥65 years), and tumor stage.

Survival analysis

For each KIF DEM, patients were divided into low- and high-expression groups according to the median expression values of each KIF genes. By utilizing survival curves by Kaplan-Meier analysis with log-rank test, we assessed the prognostic significance of every clinical aspect as well as DEM from a criterion of P<0.05. The Cox proportional hazards model was utilized for evaluating the comparative risk in such differentially expressed genes on overall survival (OS). The mRNAs significantly associated with OS in the Cox proportional hazards model were considered to be prognostic mRNAs.

Correlation analysis

Pearson correlation coefficient was assessed for identifying correlations between the prognostic mRNAs.

Joint-effects analysis and nomograms

To assess thoroughly the prognostic model, joint analysis and nomograms were performed on the KIF DEM prognostic signature. On the basis of previous survival analysis, we divided the combined genes into high-, intermediate- and low-risk groups, completed survival analysis on 3 groups of patients, and established a Cox regression model. In addition to the joint analysis, we examined the predictive prognostic value of the risk scoring using nomograms to assess the correlation among clinical status as well as risk score within BC OS. The possible implication of risk scoring on the basis of predicting clinical characteristics has similarly been discovered. C-index
and calibration curve were considered with bootstrap self-sampling and internal verification.

**Gene set enrichment analysis (GSEA)**

The core concept in GSEA is to utilize a predefined group of genes (mainly by previous experimental outcomes or functional annotations) for ranking the genes in accordance with the extent of differential expression within the 2 types of samples, then verifying that the pre-established group of genes is supplemented at the bottom or top in the sorting table. To explore the differences in pathways as well as biological functions in the low- and high-expression sets of such prognostic KIF genes, GSEA (http://software.broadinstitute.org/gsea/index.jsp, accessed August 9, 2018) [25,26] was used to explore potential KEGG pathway and GO analysis within the Molecular Signatures Database (MSigDB) of c2 (curated gene sets) and c5 (GO gene sets) [27]. The criteria for significant enrichment gene sets in GSEA were: P<0.05 and false discovery rate (FDR) <0.25.

**Statistical analysis**

Log-rank assessment was utilized for comparing clinical aspects as well as univariate survival analysis of KIF genes. Clinicopathological parameters statistically linked to OS (P<0.05) were included in multivariate Cox proportional hazard regression models to adjust. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to assess the relative risk in many patients with BC. Multiple testing with the Benjamini–Hochberg procedure was used to control the FDR in GSEA. Statistical analysis was performed using SPSS 22.0 and R 3.5.1 software. P<0.05 was considered to be statistically significant.

**Results**

**Bioinformatics analysis of the KIF family genes**

Enrichment analysis of GO terms for the KIF family genes, performed with DAVID, showed that KIF genes had suggestive enrichment for microtubule-based movement, and biological functions mainly included mitotic metaphase plate congression, mitotic cytokinesis, mitotic spindle assembly, cell division, mitotic spindle midzone assembly, and positive regulation of cytokinesis (Figure 1). Gene–gene and protein–protein interaction networks confirmed that the KIF genes had solid protein homology as well as co-expression with one another at the protein as well as gene levels (Figure 2A, 2B). The focused KIF genetic acyclic graph constructed by BINGO in Cytoscape similarly showed that the main biological roles were cell cycle progression, cellular processes, and microtubule-based processes (Figure 2C).
**Figure 1.** GO term and KEGG analysis of all the KIF family genes. GO term enrichments of KIF genes: (A) for MF; (B) for CC; (C) for BP. (D) KEGG enrichments of KIF genes. GO – gene ontology; KEGG – Kyoto Encyclopedia of Genes and Genomes; KIF – kinesin; MF – molecular function; CC – cellular component; BP – biological process.

### Patient characteristics influencing differential KIF expression in BC

The $|\log_{2} FC|$ of KIF family is shown in a histogram (Figure 3A). Thirteen KIF family genes met the standard of FDR $<0.05$ together with $|\log_{2} FC| \geq 2$ (Table 1). A scatter plot produced using TCGA showed the difference in expression of the 13 KIF genes in invasive BC tissues compared with normal breast tissues (Figure 3B). Therefore, only the remaining 13 mRNAs were included in the step function screening to investigate the optimal combination, and all the mRNA expression data were log$_{2}$ transformed for further analysis. The KIF genetic ROC analysis in the TCGA cohort specified that every KIF gene was highly accurate for discriminating normal breast and tumor tissues (area under the curve for the ROC curves in 11 KIF genes remained $>0.9$; Figure 4, Table 1).
Figure 2. Protein–protein and gene–gene interaction networks of KIF genes. (A) GeneMANIA interaction networks. (B) Protein–protein interaction networks; (C) BiNGO analysis. KIF – kinesin; BiNGO – Biological Networks Gene Ontology tool.
| Gene name | log2 fold change | P value | FDR | AUC       | 95%CI      | P value |
|-----------|-----------------|---------|-----|-----------|------------|---------|
| KIF4A     | 3.815           | 0.000   | 0.000 | 0.979     | 0.969–0.988| 0.000   |
| KIFC1     | 3.134           | 0.000   | 0.000 | 0.968     | 0.956–0.980| 0.000   |
| KIF18B    | 3.545           | 0.000   | 0.000 | 0.967     | 0.951–0.983| 0.000   |
| KIF20A    | 3.302           | 0.000   | 0.000 | 0.964     | 0.948–0.980| 0.000   |
| KIF23     | 3.352           | 0.000   | 0.000 | 0.962     | 0.949–0.975| 0.000   |
| KIF11     | 2.488           | 0.000   | 0.000 | 0.961     | 0.945–0.977| 0.000   |

Figure 3. (A) Expression of KIF family genes. (B) Gene expression distribution of KIF genes in TCGA. * P<0.01. KIF – kinesin; TCGA – the Cancer Genome Atlas.

Table 1. The difference expression between BC patients and normal breast tissues.
Table 1 continued. The difference expression between BC patients and normal breast tissues.

| Gene name | log2 fold change | P value | FDR | AUC   | 95% CI   | P value |
|-----------|------------------|---------|-----|-------|---------|---------|
| KIF14     | 3.489            | 0.000   | 0.000 | 0.955 | 0.938–0.973 | 0.000   |
| KIF22     | 1.450            | 0.000   | 0.000 | 0.950 | 0.936–0.965 | 0.000   |
| KIF15     | 2.519            | 0.000   | 0.000 | 0.943 | 0.924–0.962 | 0.000   |
| KIF18A    | 2.405            | 0.000   | 0.000 | 0.935 | 0.917–0.952 | 0.000   |
| KIF24     | 1.563            | 0.002   | 0.013 | 0.929 | 0.911–0.948 | 0.000   |
| KIF26B    | 2.793            | 0.000   | 0.000 | 0.927 | 0.909–0.944 | 0.000   |
| KIF2C     | 2.087            | 0.000   | 0.000 | 0.880 | 0.857–0.904 | 0.000   |
| KIF26A    | –1.291           | 0.006   | 0.027 | 0.867 | 0.840–0.895 | 0.000   |
| KIF13A    | –0.716           | 0.001   | 0.006 | 0.859 | 0.931–0.887 | 0.000   |
| KIF17     | –1.062           | 0.132   | 0.305 | 0.829 | 0.794–0.865 | 0.000   |
| KIF25     | –1.970           | 0.018   | 0.066 | 0.809 | 0.771–0.848 | 0.000   |
| KIF1B     | –0.693           | 0.002   | 0.013 | 0.797 | 0.763–0.832 | 0.000   |
| KIF4B     | 2.058            | 0.298   | 0.532 | 0.781 | 0.744–0.818 | 0.000   |
| KIF20B    | 0.825            | 0.027   | 0.092 | 0.765 | 0.730–0.800 | 0.000   |
| KIF19     | –0.436           | 0.534   | 0.747 | 0.757 | 0.724–0.790 | 0.000   |
| KIF1C     | –0.715           | 0.000   | 0.002 | 0.738 | 0.691–0.785 | 0.000   |
| KIF21A    | 0.815            | 0.007   | 0.032 | 0.733 | 0.699–0.767 | 0.000   |
| KIFAP3    | 0.395            | 0.096   | 0.242 | 0.720 | 0.686–0.754 | 0.000   |
| KIF5A     | –0.338           | 0.475   | 0.702 | 0.707 | 0.657–0.757 | 0.000   |
| KIF3C     | –0.346           | 0.261   | 0.486 | 0.704 | 0.664–0.743 | 0.000   |
| KIF9      | 0.507            | 0.367   | 0.605 | 0.684 | 0.645–0.724 | 0.000   |
| KIF7      | –0.322           | 0.377   | 0.616 | 0.679 | 0.637–0.721 | 0.000   |
| KIF3B     | 0.352            | 0.071   | 0.194 | 0.665 | 0.629–0.700 | 0.000   |
| KIF13B    | –0.027           | 0.815   | 0.927 | 0.626 | 0.592–0.659 | 0.000   |
| KIF3A     | 0.348            | 0.343   | 0.580 | 0.617 | 0.569–0.664 | 0.000   |
| KIF1BP    | 0.183            | 0.414   | 0.651 | 0.612 | 0.568–0.656 | 0.000   |
| KIF12     | 1.161            | 0.000   | 0.002 | 0.605 | 0.557–0.653 | 0.000   |
| KIF1A     | 4.263            | 0.000   | 0.000 | 0.604 | 0.565–0.644 | 0.000   |
| KIF27     | –0.115           | 0.693   | 0.857 | 0.598 | 0.545–0.652 | 0.001   |
| KIF3C     | 0.444            | 0.182   | 0.381 | 0.568 | 0.532–0.604 | 0.018   |
| KIF5B     | –0.040           | 0.903   | 0.977 | 0.553 | 0.504–0.601 | 0.065   |
| KIF16B    | 0.292            | 0.219   | 0.433 | 0.536 | 0.498–0.574 | 0.211   |
| KIF21B    | 0.436            | 0.437   | 0.671 | 0.510 | 0.470–0.550 | 0.722   |
| KIF6      | 0.406            | 0.772   | 0.904 | 0.509 | 0.471–0.547 | 0.765   |
| KIF2A     | 0.065            | 0.772   | 0.904 | 0.507 | 0.465–0.549 | 0.805   |
| KIF5C     | 0.742            | 0.023   | 0.083 | 0.506 | 0.463–0.550 | 0.826   |

FDR – false discovery rate; AUC – area under the curve; 95%CI – 95% confidence interval.
Survival analysis and association analysis

In the TCGA invasive BC cohort, patients with advanced tumor stage and age ≥65 years had an increased risk of invasive BC mortality (Table 2). Other patient characteristics, including gender and race, within the TCGA cohort did not show a significant association with OS of invasive BC.

Survival analysis of the 13 differentially expressed KIF genes is shown in Table 3. Patients with low expression of KIF15, KIF20A, KIF23, KIF2C and KIF4A genes in the TCGA invasive BC cohort had an extended OS (Table 3, Figure 5A–5E). However, only the KIF23 and KIF4A genes in the TCGA invasive BC cohort did not show a significant association with OS of invasive BC.

After performing survival analysis within the TCGA cohorts, co-expression analysis of KIF15, KIF20A, KIF23, KIF2C and KIF4A in BC malignant tissues was evaluated using Pearson’s correlation coefficient. The genes were co-expressed strongly with each other in the TCGA cohort (Figure 6).
Table 2. Demographic and clinical data for 1055 BC patients.

| Variables       | Patients (n=1055) | No. of events | MST (days) | HR (95% CI)       | Log-rank P |
|-----------------|-------------------|---------------|------------|------------------|------------|
| Race            |                   |               |            |                  |            |
| White           | 732               | 109           | 3941       | Ref              | 0.534      |
| Others          | 239               | 33            | 3873       | 1.132 (0.766–1.671) |            |
| Missing         | 84                |               |            |                  |            |
| Gender          |                   |               |            |                  | 0.854      |
| Female          | 1043              | 148           | 3926       | Ref              |            |
| Male            | 12                | 1             | NA         | 0.832 (0.116–5.96) |            |
| Age (years)     |                   |               |            |                  | <0.001     |
| ≥65             | 719               | 88            | 6456       | Ref              |            |
| <65             | 322               | 61            | 3418       | 2.18 (1.567–3.033) |            |
| Missing         | 14                |               |            |                  |            |
| Tumor stage     |                   |               |            |                  | <0.001     |
| I               | 175               | 15            | 3959       | Ref              |            |
| II              | 596               | 65            | 4267       | 1.71 (0.974–2.999) |            |
| III             | 241               | 43            | 3461       | 3.131 (1.738–5.641) |            |
| IV              | 20                | 15            | 1034       | 13.481 (6.572–27.654) |            |
| Missing         | 23                |               |            |                  |            |

MST – median survival time; HR – hazard ratio; CI – confidence interval.

Effect of combinations of KIF gene expression on OS

Based on KIF gene survival analysis, KIF15, KIF20A, KIF23, KIF2C and KIF4A were screened as prognostic genes by multivariate survival analysis. A joint-effects model was utilized for determining the combined influence of the 5 KIF genes on OS of BC patients. The diverse groups for this analysis were generated in accordance with expression of KIF15, KIF20A, KIF23, KIF2C and KIF4A (Tables 4–7). The Kaplan-Meier estimator with a log-rank evaluation was administered to evaluate the prognostic significance of the gene expression combinations represented by each group. Two selected groups showed that the BC patients with high expression of KIF20A and KIF4A or high expression of KIF2C and KIF4A had poor OS (Table 8). Within the evaluation of low KIF15, KIF20A, KIF23, KIF2C and low KIF4A expression, the combinations in groups 4, 7, 10, 13, 16, 19, 22, 25 and 28 were highly correlated with favorable OS (all P<0.05; Table 8). In the analysis of high expression of KIF15, KIF20A, KIF23, KIF2C and KIF4A, the combinations in groups 3, 6, 9, 12, 15, 18, 21, 24, 27 and 30 were highly correlated with poor OS (all P<0.05; Table 8).

GSEA

GSEA of the prognostic genes KIF15, KIF20A, KIF23, KIF2C and KIF4A was performed within the TCGA cohorts. The expression profiles of the genome-wide dataset in the TCGA-based cohorts were divided into 2 groups in accordance with the median prognostic KIF genetic values. GSEA outcomes of the TCGA cohort are shown in Figures 7A–7L, 8A–8L and 9A–9F, which suggested that their elevated expression remained linked with mismatch repair, P53 regulation pathway, and cell cycle progression.

Nomogram analysis

The nomogram was driven from rms as well as its supplementary packages on the base of information of patients having BC with comprehensive clinical evidence within TCGA. It showed that, among the 5 KIF genes, KIF4A had the greatest sum of risk points (ranging between 0 and 100), while the other genes made a considerably lower contribution (Figure 10A). By examining the conformity and discrimination using the nomogram model, bootstrap analysis on the bases of 1000 resampling tests had a C-index of 0.76 and 95% CI of 0.70–0.82. The discrimination is suitable. The calibration curve showed that the general point was close to the ideal curve of 45 degrees, indicating good compliance (Figure 10B, 10C).
Table 3. Prognostic survival analysis according to the high or low level of 13 diagnostic KIF genes and OS.

| Gene   | Patients (n=1055) | Events | MST (days) | Crude HR (95% CI) | Crude P | Adjusted HR* (95% CI)* | Adjusted P* |
|--------|-------------------|--------|------------|-------------------|---------|------------------------|-------------|
| KIF11  |                   |        |            |                   |         |                        |             |
| High   | 527               | 82     | 4456       | 1                 |         |                        |             |
| Low    | 528               | 67     | 3736       | 1.106 (0.801–1.529) | 0.54    | 1.402 (0.991–1.982)     | 0.056       |
| KIF14  |                   |        |            |                   |         |                        |             |
| High   | 527               | 76     | 7455       | 1                 |         |                        |             |
| Low    | 528               | 73     | 3736       | 1.028 (0.745–1.417) | 0.869   | 1.187 (0.848–1.663)     | 0.318       |
| KIF15  |                   |        |            |                   |         |                        |             |
| High   | 527               | 80     | 6593       | 1                 |         |                        |             |
| Low    | 528               | 69     | 3736       | 1.068 (0.773–1.476) | 0.688   | 1.422 (1.007–2.008)     | 0.045       |
| KIF1A  |                   |        |            |                   |         |                        |             |
| High   | 527               | 82     | 3945       | 1                 |         |                        |             |
| Low    | 528               | 71     | 3736       | 1.143 (0.829–1.577) | 0.415   | 1.224 (0.875–1.713)     | 0.238       |
| KIF1C  |                   |        |            |                   |         |                        |             |
| High   | 527               | 74     | 3945       | 1                 |         |                        |             |
| Low    | 528               | 75     | 3926       | 1.001 (0.726–1.38) | 0.996   | 1.046 (0.748–1.461)     | 0.794       |
| KIF20A |                   |        |            |                   |         |                        |             |
| High   | 527               | 87     | 3959       | 1                 |         |                        |             |
| Low    | 528               | 62     | 3736       | 1.273 (0.917–1.766) | 0.148   | 1.467 (1.038–2.072)     | 0.03        |
| KIF23  |                   |        |            |                   |         |                        |             |
| High   | 527               | 83     | 3959       | 1                 |         |                        |             |
| Low    | 528               | 66     | 3736       | 1.23 (0.889–1.701) | 0.21    | 1.54 (1.09–2.175)       | 0.014       |
| KIF26B |                   |        |            |                   |         |                        |             |
| High   | 527               | 69     | 3472       | 1                 |         |                        |             |
| Low    | 528               | 80     | 3959       | 1.067 (0.771–1.475) | 0.696   | 1.194 (0.848–1.682)     | 0.309       |
| KIF2C  |                   |        |            |                   |         |                        |             |
| High   | 527               | 84     | 3959       | 1                 |         |                        |             |
| Low    | 528               | 65     | 3926       | 1.341 (0.97–1.855) | 0.075   | 1.805 (1.276–2.553)     | 0.001       |
| KIF4A  |                   |        |            |                   |         |                        |             |
| High   | 527               | 90     | 3941       | 1                 |         |                        |             |
| Low    | 528               | 59     | 3926       | 1.557 (1.121–2.162) | 0.008   | 1.805 (1.276–2.553)     | 0.001       |
| KIFC1  |                   |        |            |                   |         |                        |             |
| High   | 527               | 82     | 4456       | 1                 |         |                        |             |
| Low    | 528               | 67     | 3492       | 1.006 (0.798–1.334) | 0.545   | 1.273 (0.902–1.786)     | 0.17        |
| KIFC2  |                   |        |            |                   |         |                        |             |
| High   | 527               | 71     | 4456       | 1                 |         |                        |             |
| Low    | 528               | 78     | 3669       | 0.983 (0.712–1.358) | 0.919   | 0.915 (0.683–1.281)     | 0.603       |

* Adjusted for age (stratified by 65 years) and tumor stage. KIF – kinesin; OS – overall survival; MST – median survival time; HR – hazard ratio; CI – confidence interval.
Discussion

Kinesin motor activity is spatially as well as temporally controlled within mitosis to ensure that it occurs precisely with stable inward and outward forces. Nevertheless, over-expression of a few mitotic kinesins might produce further outward forces. This provokes a sequence of undesirable events, such as overshooting before anaphase, sister chromatid segregation before anaphase, increased spindle separation, and ultimately monopolar or bipolar spindle formation [28]. Such things might cause imbalanced distribution of DNA, aneuploidy and a plethora of cancer phenotypes, together with metastatic and invasive behavior. Kinesin function might cause failed cytokinesis, imperfect spindle assembly and mitotic arrest, which stimulates apoptosis and killing of cancer cells [15]. Our evaluation of genetic function enrichment suggested that the KIF gene family is involved in biological processes of the cell cytoplasm such as mitotic cytokinesis, mitotic spindle assembly, and positive regulation of cytokinesis. Our analysis established that KIF15, KIF20A, KIF23, KIF2C, and KIF4A were co-expressed at the protein and gene levels.

Figure 5. Kaplan-Meier survival curves for KIF genes in BC of TCGA cohort. OS stratified by KIF15 (A), KIF20A (B), KIF23 (C), KIF2C (D), and KIF4A (E). KIF – kinesin; TCGA – the Cancer Genome Atlas; BC – breast cancer; OS – overall survival.
Table 4. Grouping according to 2 selected genes.

| Group | Combination            | Group | Combination            |
|-------|------------------------|-------|------------------------|
| 1     | Low KIF15 + low KIF20A | 16    | Low KIF20A + low KIF2C |
| 2     | Low KIF15 + high KIF20A| 17    | Low KIF20A + high KIF2C|
| 3     | High KIF15 + low KIF20A| 18    | High KIF20A + low KIF2C|
| 4     | Low KIF15 + low KIF23  | 19    | Low KIF20A + low KIF4A |
| 5     | Low KIF15 + high KIF23 | 20    | Low KIF20A + high KIF4A|
| 6     | High KIF15 + low KIF23 | 21    | High KIF20A + low KIF4A|
| 7     | Low KIF15 + low KIF2C  | 22    | Low KIF23 + low KIF2C  |
| 8     | Low KIF15 + high KIF2C | 23    | Low KIF23 + high KIF2C |
| 9     | High KIF15 + high KIF2C| 24    | High KIF23 + high KIF2C|
| 10    | Low KIF15 + low KIF4A  | 25    | Low KIF23 + low KIF4A  |
| 11    | Low KIF15 + high KIF4A | 26    | Low KIF23 + high KIF4A |
| 12    | High KIF15 + low KIF4A | 27    | High KIF23 + high KIF4A|
| 13    | Low KIF20A + low KIF23 | 28    | Low KIF2C + low KIF4A  |
| 14    | Low KIF20A + high KIF23| 29    | Low KIF2C + high KIF4A |
| 15    | High KIF20A + low KIF23| 30    | High KIF2C + high KIF4A|

KIF – kinesin.

Figure 6. Co-expression heat map of KIF2C, KIF4A, KIF23, KIF20A and KIF15 in TCGA BC patients. KIF – kinesin; TCGA – the Cancer Genome Atlas; BC – breast cancer.
### Table 5. Grouping according to 3 selected genes.

| Group | Combination                      | Group | Combination                      |
|-------|----------------------------------|-------|----------------------------------|
| a     | Low KIF15 + low KIF20A + low KIF23 | A     | Low KIF15 + low KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + low KIF23 |       | High KIF15 + low KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + low KIF23 |       | Low KIF15 + low KIF2C + low KIF4A |
| b     | Low KIF15 + high KIF20A + low KIF23 | B     | High KIF15 + high KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + low KIF23 |       | High KIF15 + low KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + high KIF23 |     | Low KIF15 + low KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF15 + low KIF2C + low KIF4A |
| c     | High KIF15 + high KIF20A + high KIF23 | C     | High KIF15 + high KIF2C + high KIF4A |
| d     | Low KIF15 + low KIF20A + low KIF2C | D     | Low KIF20A + low KIF23 + low KIF2C |
|       | High KIF15 + high KIF20A + high KIF23 |     | Low KIF20A + low KIF23 + low KIF2C |
|       | Low KIF15 + high KIF20A + low KIF2C | E     | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |
|       | Low KIF15 + low KIF20A + low KIF2C |       | Low KIF20A + high KIF23 + low KIF2C |

KIF – kinesin.
### Table 6. Grouping according to 4 selected genes.

| Group | Combination | Group | Combination |
|-------|-------------|-------|-------------|
| I     | Low KIF15 + low KIF20A + low KIF23 + low KIF2C | X     | Low KIF15 + low KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + high KIF20A + low KIF23 + low KIF2C |       | High KIF15 + low KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + high KIF23 + high KIF2C |       | High KIF15 + high KIF23 + high KIF2C + high KIF4A |
| II    | High KIF15 + high KIF20A + low KIF23 + high KIF2C | XI    | Low KIF15 + high KIF23 + high KIF2C + low KIF4A |
|       | High KIF15 + high KIF20A + high KIF23 + low KIF2C |       | Low KIF15 + high KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + high KIF23 + high KIF2C |       | Low KIF15 + low KIF23 + high KIF2C + low KIF4A |
|       | High KIF15 + high KIF20A + low KIF23 + high KIF2C |       | Low KIF15 + low KIF23 + low KIF2C + low KIF4A |
| IV    | Low KIF15 + high KIF20A + low KIF23 + low KIF4A | XIII  | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + high KIF20A + low KIF23 + low KIF4A |       | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + high KIF23 + low KIF4A |       | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + high KIF23 + low KIF4A |       | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + high KIF23 + low KIF4A |       | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
| V     | Low KIF15 + high KIF20A + high KIF23 + low KIF4A | XIV   | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + low KIF23 + high KIF4A |       | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + low KIF23 + high KIF4A |       | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
| VI    | High KIF15 + high KIF20A + high KIF23 + high KIF4A | XV    | High KIF20A + high KIF23 + high KIF2C + high KIF4A |
| VII   | Low KIF15 + low KIF20A + low KIF2C + low KIF4A |       | Low KIF20A + low KIF23 + low KIF2C + low KIF4A |
We found 5 KIF genes of diagnostic and prognostic value. Extensive studies have reported these genes as potential diagnostic markers in multiple cancers. Among the 5 genes, KIF15 is likewise overexpressed in lung adenocarcinoma and might play a significant role in modifying the cell cycle [29]. Likewise, KIF15 promotes proliferation of pancreatic cancer cells via the MEK/ERK pathway [30]. KIF15 is overexpressed in BC cells and might have potential as a novel therapeutic target and a prognostic factor in endocrine-therapy-resistant BC [31]. We found that expression of KIF15 mRNA was significantly higher in BC than in adjacent tissues, and elevated expression of KIF15 in patients with BC was associated with poor OS. Our results agreed with previous studies that designated the KIF15 as an oncogene in BC.

In 2005, a study by Keisuke et al. [32] found that KIF20A was overexpressed in pancreatic cancer according to cDNA microarray analysis, and down-regulation of KIF20A significantly decreased tumor cell proliferation, confirming that KIF20A is carcinogenic in pancreatic cancer. Numerous studies have shown that KIF20A also has carcinogenic traits in various other cancers, such as nasopharyngeal carcinoma, liver cancer, melanoma, lung adenocarcinoma and glioma [33]. It has been suggested that the KIF20A gene is a potential diagnostic biomarker. We found that KIF20A has differential expression in BC and adjacent tissues, and high expression of KIF20A is related to poor OS in patients with BC, so it might also be a prognostic biomarker.

It has been found that KIF23 is up-regulated in patients with hepatocellular carcinoma, and it may be a marker for OS [34]. Zou et al. [31] showed that KIF4A, KIF15, KIF20A and KIF23 expression was significant in proliferating BC cells. They also showed that, among patients treated with tamoxifen, high expression of these 4 genes was highly correlated with poor recurrence-free survival. It has been suggested that over-expression of KIF23 is a valuable independent prognostic factor in lung tumors, particularly lung adenocarcinoma, and patients with p-stage I tumor stage and high expression of KIF23 have poorer survival than those with low expression [35]. In addition, the multivariate Cox proportional hazards model in our study, which was based on expression of KIF23, likewise divided patients in low- and high-expression groups, and patients with high expression had poor OS.

Nowadays, it is certain that KIF4A performs a significant role in cancer development and progression. Numerous studies have shown that KIF4A is a potential contributor to several malignant tumors, such as lung cancer [36], breast cancer [37], cervical cancer [38], hepatocellular carcinoma [39], and oral cancer [40]. Our results were consistent with previous studies. We also found that BC patients with high expression of KIF4A had poor OS compared with patients with low expression.
| Group | Combination |
|-------|-------------|
| 1     | Low KIF15 + low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + high KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + high KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + low KIF23 + low KIF2C + high KIF4A |
|       | High KIF15 + low KIF20A + high KIF23 + low KIF2C + low KIF4A |
| 2     | Low KIF15 + low KIF20A + low KIF23 + high KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + low KIF23 + low KIF2C + high KIF4A |
|       | Low KIF15 + low KIF20A + high KIF23 + low KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + low KIF23 + high KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + high KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + low KIF23 + high KIF2C + low KIF4A |
| 3     | Low KIF15 + low KIF20A + low KIF23 + low KIF2C + high KIF4A |
|       | Low KIF15 + high KIF20A + low KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + low KIF23 + high KIF2C + low KIF4A |
|       | Low KIF15 + low KIF20A + low KIF23 + low KIF2C + high KIF4A |
|       | High KIF15 + low KIF20A + low KIF23 + high KIF2C + low KIF4A |
|       | High KIF15 + low KIF20A + high KIF23 + low KIF2C + low KIF4A |
|       | Low KIF15 + high KIF20A + low KIF23 + high KIF2C + low KIF4A |

KIF = kinesin.
| Group | Patients | MST (days) | Crude p | Crude HR | Adjusted p | Adjusted HR (95% CI) * |
|-------|----------|------------|---------|----------|------------|------------------------|
| 1     | 432      | 3736       | 0.367   | 1        | 0.065      | 1                      |
| 2     | 192      | 3941       | 0.185   | 1.354    | 0.16       | 1.419 (0.87–2.313)     |
| 3     | 431      | 6593       | 0.291   | 1.219    | 0.021      | 1.578 (1.07–2.322)     |
| 4     | 444      | 3669       | 0.439   | 1        | 0.001      |                        |
| 5     | 168      | 4456       | 0.229   | 1.328    | 0.223      | 1.363 (0.82–2.245)     |
| 6     | 443      | 3959       | 0.356   | 1.184    | 0.014      | 1.615 (1.1–2.372)      |
| 7     | 428      | 3736       | 0.398   | 1        | 0.001      |                        |
| 8     | 200      | 6456       | 0.279   | 1.296    | 0.021      | 1.825 (1.09–3.037)     |
| 9     | 427      | 3959       | 0.23    | 1.244    | 0.003      | 1.776 (1.21–2.604)     |
| 10    | 436      | 3669       | 0.237   | 1        | 0.013      |                        |
| 11    | 184      | 6456       | 0.396   | 1.223    | 0.196      | 1.39 (0.84–2.29)       |
| 12    | 435      | 3873       | 0.09    | 1.369    | 0.003      | 1.787 (1.21–2.63)      |
| 13    | 450      | 3736       | 0.292   | 1        | 0.038      |                        |
| 14    | 156      | 3461       | 0.265   | 1.318    | 0.116      | 1.508 (0.94–2.517)     |
| 15    | 445      | 3959       | 0.14    | 1.308    | 0.003      | 1.625 (1.12–2.374)     |
| 16    | 441      | 3736       | 0.221   | 1        | 0.008      |                        |
| 17    | 174      | 4456       | 0.546   | 1.169    | 0.652      | 1.133 (0.65–1.949)     |
| 18    | 440      | 3959       | 0.083   | 1        | 0.005      | 1.715 (1.18–2.503)     |
| 19    | 454      | 3736       | 0.051   | 1        | 0.011      |                        |
| 20    | 148      | 6593       | 0.772   | 0.919    | 0.735      | 1.114 (0.59–2.074)     |
| 21    | 453      | 4456       | 0.398   | 1.463    | 0.004      | 1.715 (1.18–2.475)     |
| 22    | 445      | 3736       | 0.207   | 1        | 0.006      |                        |
| 23    | 166      | 3941       | 0.197   | 1.379    | 0.394      | 1.258 (0.74–2.131)     |
| 24    | 444      | 3959       | 0.101   | 1.344    | 0.002      | 1.844 (1.26–2.696)     |
| 25    | 453      | 3736       | 0.070   | 1        | 0.004      |                        |
| 26    | 150      | 3959       | 0.289   | 0.938    | 0.932      | 1.026 (0.57–1.837)     |
| 27    | 452      | 3941       | 0.040   | 1.436    | 0.002      | 1.787 (1.24–2.585)     |
| 28    | 457      | 3736       | 0.033   | 1        | 0.001      |                        |
| 29    | 142      | 4456       | 0.751   | 0.909    | 0.457      | 1.078 (0.61–1.848)     |
| 30    | 456      | 3873       | 0.020   | 1.503    | 0.001      | 1.93 (1.34–2.78)       |
| a     | 402      | 3736       | 0.343   | 1        | 0.042      |                        |
| b     | 258      | 3941       | 0.157   | 1.354    | 0.002      | 1.466 (0.93–2.302)     |
| c     | 395      | 3959       | 0.298   | 1.225    | 0.013      | 1.674 (1.11–2.516)     |
| d     | 390      | 3736       | 0.37    | 1        | 0.04       |                        |
| e     | 283      | 3941       | 0.232   | 1.296    | 0.129      | 1.426 (0.90–2.254)     |
| f     | 382      | 3959       | 0.211   | 1.274    | 0.011      | 1.675 (1.12–2.497)     |
| g     | 399      | 3736       | 0.335   | 1        | 0.028      |                        |
| h     | 262      | 4456       | 0.45    | 1.181    | 0.225      | 1.335 (0.83–2.131)     |
| i     | 394      | 3959       | 0.139   | 1.328    | 0.008      | 1.713 (1.15–2.548)     |
| j     | 399      | 3669       | 0.34    | 1        | 0.018      |                        |
| k     | 267      | 4456       | 0.168   | 1.348    | 0.088      | 1.487 (0.94–2.346)     |

*Table 8. Joint analysis of the prognostic value of combination of KIF15, KIF20A, KIF23, KIF2C, and KIF4A expression of BC.*
Table 8 continued. Joint analysis of the prognostic value of combination of KIF15, KIF20A, KIF23, KIF2C, and KIF4A expression of BC.

| Group | Patients | MST (days) | Crude p | Crude HR (95% CI) | Adjusted p | Adjusted HR (95% CI) *
|-------|----------|------------|---------|-------------------|------------|----------------------|
| I     | 389      | 3959       | 0.262   | 1.24 (0.851–1.805) | 0.005      | 1.787 (1.193–2.675)  |
| m     | 403      | 3669       | 0.44    | 1                 | 0.019      | 1                    |
| n     | 251      | 6456       | 0.519   | 1.154 (0.747–1.782) | 0.316      | 1.267 (0.798–2.011)  |
| α     | 401      | 3873       | 0.2     | 1.275 (0.879–1.849) | 0.006      | 1.763 (1.181–2.631)  |
| A     | 398      | 3669       | 0.334   | 1                 | 0.018      | 1                    |
| B     | 263      | 6456       | 0.558   | 1.14 (0.735–1.767) | 0.315      | 1.273 (0.795–2.04)   |
| C     | 394      | 3959       | 0.141   | 1.321 (0.912–1.913) | 0.005      | 1.749 (1.18–2.593)   |
| D     | 311      | 311       | 0.424   | 1                 | 0.01       | 1                    |
| E     | 248      | 3941       | 0.312   | 1.252 (0.809–1.937) | 0.316      | 1.269 (0.797–2.023)  |
| F     | 396      | 6456       | 0.225   | 1.258 (0.869–1.821) | 0.007      | 1.721 (1.158–2.559)  |
| G     | 419      | 3736       | 0.2     | 1                 | 0.023      | 1                    |
| H     | 227      | 6593       | 0.885   | 1.035 (0.649–1.651) | 0.46       | 1.204 (0.735–1.973)  |
| I     | 409      | 3941       | 0.096   | 1.358 (0.947–1.949) | 0.007      | 1.691 (1.151–2.484)  |
| J     | 414      | 3736       | 0.081   | 1                 | 0.002      | 1                    |
| K     | 232      | 4456       | 0.964   | 0.989 (0.613–1.597) | 0.97       | 0.99 (0.591–1.658)   |
| L     | 409      | 3873       | 0.046   | 1.44 (1.006–2.061) | 0.002      | 1.823 (1.248–2.664)  |
| M     | 419      | 3736       | 0.218   | 1                 | 0.001      | 1                    |
| N     | 229      | 4456       | 0.891   | 1.033 (0.646–1.653) | 0.965      | 0.989 (0.6–1.629)    |
| O     | 407      | 3959       | 0.103   | 1.346 (0.942–1.925) | 0.002      | 1.865 (1.268–2.742)  |
| I     | 375      | 3736       | 0.391   | 1                 | 0.044      | 1                    |
| II    | 324      | 3941       | 0.179   | 1.324 (0.879–1.995) | 0.103      | 1.44 (0.929–2.231)   |
| III   | 356      | 3959       | 0.353   | 1.203 (0.815–1.777) | 0.013      | 1.693 (1.115–2.569)  |
| IV    | 381      | 3736       | 0.477   | 1                 | 0.038      | 1                    |
| V     | 304      | 4456       | 0.338   | 1.224 (0.81–1.852) | 0.189      | 1.347 (0.864–2.099)  |
| VI    | 370      | 3959       | 0.254   | 1.252 (0.851–1.843) | 0.01       | 1.715 (1.135–2.593)  |
| VII   | 375      | 3736       | 0.381   | 1                 | 0.027      | 1                    |
| VIII  | 315      | 4456       | 0.376   | 1.208 (0.795–1.837) | 0.186      | 1.355 (0.864–2.124)  |
| IX    | 365      | 3959       | 0.169   | 1.309 (0.892–1.921) | 0.01       | 1.701 (1.135–2.55)   |
| X     | 381      | 3669       | 0.544   | 1                 | 0.026      | 1                    |
| XI    | 306      | 4456       | 0.441   | 1.178 (0.776–1.789) | 0.257      | 1.294 (0.829–2.02)   |
| XII   | 368      | 3959       | 0.285   | 1.231 (0.841–1.801) | 0.007      | 1.752 (1.163–2.638)  |
| XIII  | 394      | 3736       | 0.41    | 1                 | 0.015      | 1                    |
| XIV   | 287      | 3941       | 0.553   | 1.138 (0.742–1.745) | 0.479      | 1.179 (0.747–1.859)  |
| XV    | 374      | 3959       | 0.182   | 1.29 (0.887–1.876) | 0.006      | 1.768 (1.182–2.645)  |
| O     | 364      | 3736       | 0.455   | 1                 | 0.005      | 1                    |
| ⊙     | 348      | 3941       | 0.24    | 1.275 (0.85–1.912) | 0.128      | 1.4 (0.908–2.158)    |
| ⊙     | 343      | 3959       | 0.316   | 1.224 (0.824–1.816) | 0.013      | 1.708 (1.119–2.606)  |

* Adjusted for age (stratified by 65 years) and tumor stage. KIF – kinesin; OS – overall survival; MST – median survival time; HR – hazard ratio; CI: confidence interval.
Figure 7. A–F shows GSEA of KIF2C in TCGA patients. (A–D) GSEA results of c2 reference gene sets for high KIF2C expression groups, (E–F) GSEA results of c2 reference gene sets for high KIF2C expression groups; G–L shows GSEA of KIF4A in TCGA patients. (G–J) GSEA results of c2 reference gene sets for high KIF4A expression groups; (K–L) GSEA results of c5 reference gene sets for high KIF4A expression groups. KIF – kinesin; GSEA – gene set enrichment analysis; TCGA – the Cancer Genome Atlas; BC – breast cancer.
Figure 8. A–F shows GSEA of KIF15 in TCGA patients. (A–D) GSEA results of c2 reference gene sets for high KIF15 expression groups. (E–F) GSEA results of c5 reference gene sets for high KIF15 expression groups. G–L shows GSEA of KIF20A in TCGA patients. (G–J) GSEA results of c2 reference gene sets for high KIF20A expression groups. (K–L) GSEA results of c5 reference gene sets for high KIF20A expression groups. KIF – kinesin, GSEA – gene set enrichment analysis, TCGA – the Cancer Genome Atlas, BC – breast cancer.
The present study had a few limitations. First, all the information was obtained from open databases, and the medical parameters were not complete. Therefore, we were not able to perform a far-reaching survival analysis of KIF genes, considering each latent prognostic variable of BC in the multivariate Cox proportional hazards regression model. Second, because of the varied origin of BC patients, together with the number of elements affecting BC prognosis, we were not able to construct a comprehensive hazard score model, which depended on the KIF genes articulation level for visualization forecast. Third, with the help of the correlation with the past research work, the constraint of our present investigation suggested that it just researched the relationship existing between the mRNA expression of the KIF genes and BC prognosis. Nonetheless, the connection between KIF protein level and BC requires additional investigation.

In spite of the above limitations, we established and validated the prognostic and diagnostic values of expression of KIF genes in BC patients, and similarly examined the potential mechanism linked with KIF4A, KIF15, KIF20A, KIF23 and KIF2C within BC prognosis by GSEA. When these outcomes are confirmed, the prognostic and diagnostic standards of KIF genetics on the extent of protein, such genes might hold a substantial clinical implication value in diagnosis of BC, as well as targeted therapy. Nevertheless, future verification with a larger study.
population is required to confirm that the KIF genes could be involved in diagnosis and prognostic monitoring of BC.

Conclusions

We revealed that 13 KIF genes were differentially expressed in BC tumor tissues, and may serve as latent diagnostic biomarkers in patients with BC. *KIF15, KIF20A, KIF23, KIF2C* and *KIF4A* have the potential to serve as prognostic biomarkers in patients with BC. Multivariate survival analysis, nomograms, and joint survival analysis showed high expression of these genes correlated with poor prognosis of BC. GO, KEGG and GSEA suggested that these genes affect the prognosis of BC by influencing the cell cycle. Our results need to be confirmed in further research.

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Conflicts of interest

None.