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# Identification of prognostic genes for early basal-like breast cancer with weighted gene co-expression network analysis

Keyu Yuan, MD[a], Min Wu, PhD[a], Shuzhen Lyu, MD[a], Yanping Li, MD[a,*]

**Abstract**

**Background:** Breast cancer (BC) has become the leading cause of death for women's malignancies and increasingly threatens the health of women worldwide. However, there is a lack of effective targeted drugs for basal-like BC. Therefore, biomarkers related to the prognosis of early BC need to be identified.

**Methods:** The RNA-seq data of 87 cases of early basal-like BC and 111 cases of normal breast tissue from The Cancer Genome Atlas were explored by the weighted gene co-expression network analysis method and Limma package. Then, intersected genes were identified, and hub genes were selected by the maximal clique centrality method. The prognostic effect of the hub genes was also evaluated in early basal-like BC.

**Results:** In total, 601 IGs were identified in this study. An APPI network was constructed, and the top 10 hub genes were selected, namely, cyclin B1, cyclin A2, cyclin-dependent kinase 1, cell division cycle 20, DNA topoisomerase II alpha, BUB1 mitotic checkpoint serine/threonine kinase, aurora kinase B (AURKB), cyclin B2, kinesin family member 11, and assembly factor for spindle microtubules. Only AURKB was found to be significantly associated with the overall prognosis of early basal-like BC. The immune cell infiltration analysis showed that the infiltration numbers of CD4 + T cells and naïve CD8 + T cells were positively correlated with the AURKB expression level, while those of naïve B cells and macrophage M2 cells were negatively correlated with the AURKB expression level in basal-like BC.

**Conclusion:** AURKB might be a potential prognostic indicator in early basal-like BC.

**Abbreviations:** ASPM = assembly factor for spindle microtubules, AURKB = aurora kinase B, BC = breast cancer, BUB1 = BUB1 mitotic checkpoint serine/threonine kinase, CCNA2 = cyclin A2, CCNB2 = cyclin B2, CDC20 = cell division cycle 20, DEGs = differentially expressed genes, IGs = intersected genes, TCGA = The Cancer Genome Atlas, WGCNA = weighted gene co-expression network analysis.

**Keywords:** basal-like, breast cancer, early stage, prognosis

## 1. Introduction

Breast cancer (BC) is the most common malignant tumor in females and seriously undermines the health of women worldwide. It was predicted that approximately 287,850 female patients would be diagnosed with BC and that 43,250 BC patients would die in 2022 in the US.[1] Moreover, it was reported that the incidence and mortality rates of female breast cancer in China were 16.42/100,000 and 0.66/100,000, respectively.[2] The potential risk factors for BC have been proven to be as follows: family susceptibility, hormone exposure, aging, and unhealthy lifestyle.[3–5] For early diagnosis and treatment, auxiliary examinations have developed rapidly. The most frequently used methods in clinical diagnosis are mammography, ultrasound, and MRI examination.[6] The common treatments of BC include surgical resection, chemotherapy, radiotherapy, and endocrine therapy. Furthermore, molecular targeted therapy and immunotherapy have also led to marked improvements.[7–9] The above treatments are very important in the clinic.

The prognosis and survival of BC have improved with the continuous improvement of medicine. In 2000, according to Perou's research results, BC was divided into 4 types: luminal subtype, HER-2 overexpression subtype, basal-like subtype, and normal breast-like subtype.[10] Therefore, the therapeutic guidelines and consensus of BC are mainly based on molecular classification. Basal-like BC is highly invasive and lacks effective target drugs. Currently, some biomarkers are used in BC, such as CEA, CA125, and CA153, but effective prognostic indicators are still lacking in basal-like BC.

*KY and SLKY and MW contributed equally to this work.*

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*All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The datasets generated during and/or analyzed during the current study are publicly available.*

*Supplemental Digital Content is available for this article.*

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Exploring the potential prognostic factors that could predict the survival of basal-like BC and provide higher-intensity necessary treatments is extremely important.[11] Changes in genomes have been commonly found in basal-like BCs and may affect the effectiveness of targeted therapy and the long-term prognosis. Improvements in genome testing are helpful for identifying genes related to prognosis and promoting the development of new drugs. Compared to pathological inspection, genome detection is more direct to the root of the disease and the biological characteristics, and it handles the problem that clinical parameters cannot perfectly reflect. Furthermore, compared to pathological biopsy, more information could be provided in a shorter time by new second-generation sequencing technology. This study aimed to explore the biomarkers that affect the prognosis of BLBC from the perspective of biometric analysis.

## 2. Methods

### 2.1. Differentially expressed genes identified

The RNA-seq data of early basal-like BC and normal breast tissue were downloaded and then selected from The Cancer Genome Atlas (TCGA) database (https://tcga-data.nci.nih.gov/tcga). The clinical data of early basal-like BC were also obtained from the TCGA database, and only early basal-like BC with prognostic data were included in the following analysis. Ethical approval was not necessary for this study because public datasets were analyzed. In this study, early basal-like BC was identified as basal-like BC with the American Joint Committee on Cancer TNM Staging System (AJCC TNM, 2018 Edition) stage I and IIA. The differentially expressed genes (DEGs) were identified using the Edge R and Limma package in R software. The criteria were defined as adjusted $P$ value ≤ 0.05 and $|Log_2FC| \geq 1$. Consent was unnecessary for the TCGA data used in this study.

### 2.2. Weighted gene co-expression network analysis

The gene expression dataset of early basal-like BC and normal breast tissue was further explored using the weighted gene co-expression network analysis (WGCNA) method. WGCNA is a systematic method that describes the gene correlation patterns in microarray samples. The WGCNA included functions of network construction, module selection, gene selection, and topological property calculations.[12] The genes in the WGCNA module with the highest correlation value and most significance were further intersected with the DEGs. The genes that overlapped in DEGs and WGCNA modules were defined as intersected genes (IGs).

### 2.3. Functional analysis of IGs

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses of IGs were carried out on the Database for Annotation, Visualization, and Integrated Discovery v6.8 (https://david.ncifcrf.gov/). The Gene Ontology functional analysis included 3 categories: biological process, cellular components, and molecular function. The terms with a $P$ value ≤ 0.05 were considered significant.

### 2.4. Identifying the hub IGs and evaluating their prognostic effect

Before identifying the hub IGs, the protein–protein internetwork of IGs was constructed with the STRING website (https://www.string-db.org/) and Cytoscape V3.7.2 (Boston, MA). Then, the top 10 hub IGs were selected by applying the maximal clique centrality method in Cytoscape software. The hub IGs significantly associated with prognosis were screened out using the survival package in R software (Vienna, Austria) with the criteria of $P$ value < 0.05 and hazard ratio > 1. Furthermore, the expression levels of prognosis-associated IGs were validated in the Tumor Immune Estimation Resource (TIMER)TIMER dataset (http://cistrome.dfci.harvard.edu/TIMER/), and their relationship with immune cell infiltration in basal-like BC was also analyzed.

## 3. Results

### 3.1. IGs identified in early basal-like BC

The heatmap of gene expression differences between 87 cases of early basal-like BC and 111 cases of normal breast tissues is presented in Figure 1A. Then, 1465 DEGs were identified in early

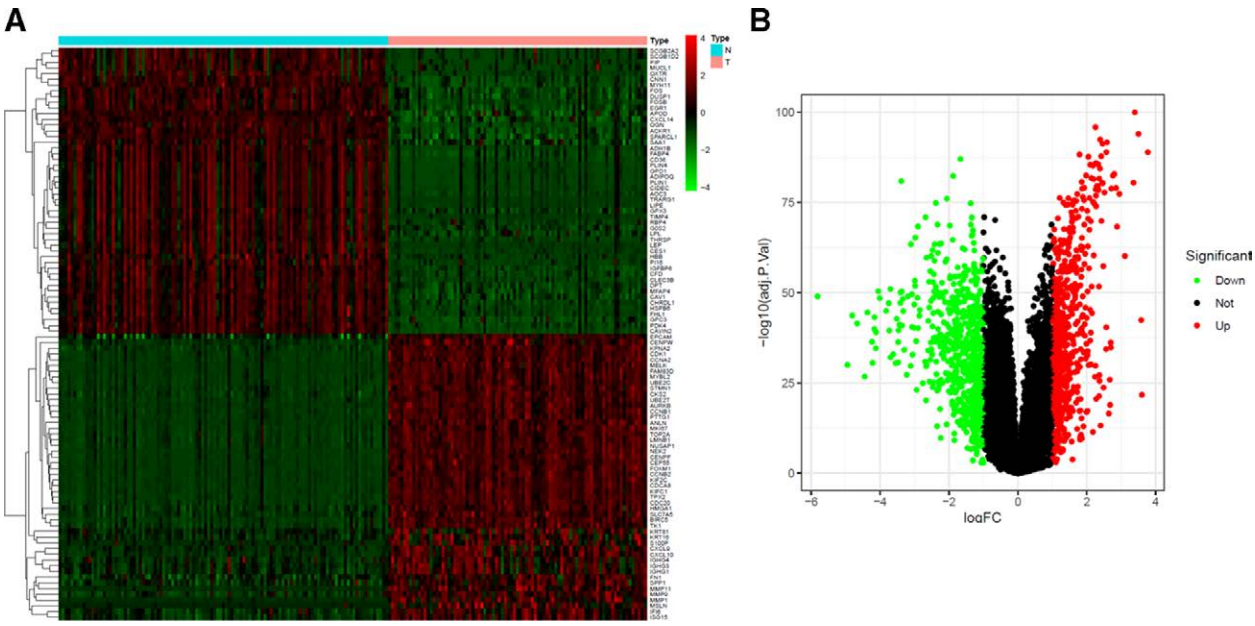


**Figure 1.** Heatmap and volcano plot of the differentially expressed genes in early-stage BLBC. Type: N, normal tissues; T, breast cancer; Green, low expression; Red, high expression. BLBC = basal-like breast cancer.

basal-like BC, as shown in Figure 1B. The scale independence and mean connectivity of WGCNA are shown in Figure 2A. After WGCNA, 16 modules were obtained (Fig. 2B). The turquoise module with the highest correlation coefficient (cor. = 0.96, *P* value < 2e-107) and most significance was selected for the following analysis (Fig. 2C). The correlation between module membership and gene significance in the turquoise module was 0.98 with a *P* value < 1.0e-200 (Fig. 2D). By intersecting the DEGs and the genes in the turquoise module, 601 IGs were identified (Fig. 3A).

### 3.2. Functional analysis of IGs

The functional analysis results of IGs are presented in Table 1. In the biological process category, IGs were mainly enriched in cell division, mitotic nuclear division, and cell proliferation. In the cellular components category, IGs were mainly enriched in the nucleus, cytoplasm, and cytosol. In the molecular function category, IGs were mainly enriched in protein binding, ATP binding, and poly(A) RNA binding. IGs were mostly enriched in pathways including the cell cycle, p53 signaling pathway, and DNA replication.

### 3.3. Hub IG selection and protein-protein interaction (PPI) network building

A PPI network with 519 nodes and 520 edges was built (Figure S1, Supplemental Digital Content 1, http://links.lww.com/MD/H320). The PPI enrichment *P* value and average local clustering coefficient were < 1.0e-16 and 0.338, respectively. Then, the top 10 hub genes were selected by the maximal clique centrality method, namely, cyclin B1, cyclin A2 (CCNA2), cyclin-dependent kinase 1, cell division cycle 20 (CDC20), DNA topoisomerase II alpha, BUB1 mitotic checkpoint serine/threonine kinase (BUB1), aurora kinase B (AURKB), cyclin B2 (CCNB2), kinesin family member 11, and assembly factor for spindle microtubules (ASPM) (Fig. 3B). The specificity of the above hub genes among BC subtypes at an early stage was also analyzed. Compared to normal tissues and luminal A- and HER-2-enriched BC, the expression of hub genes was significantly upregulated in basal-like BC (*P* < .001) (Fig. 4A). The sex genes (CCNA2, CDC20, BUB1, AURKB, CCNB2, and ASPM) were highly expressed in basal-like BC compared to luminal B BC (*P* < .001) (Fig. 4A and B).

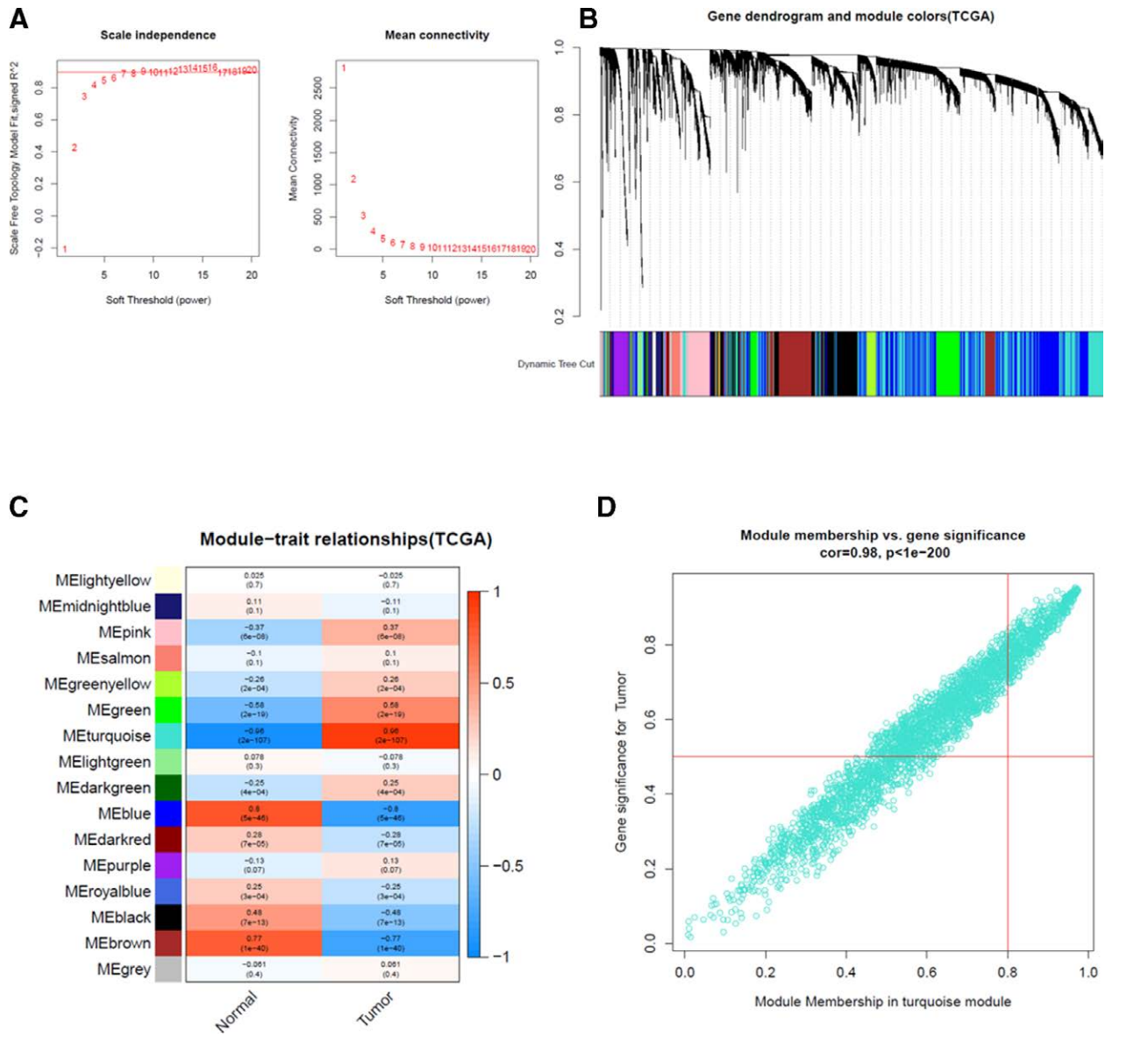


**Figure 2.** Weighted gene co-expression network analysis results of early-stage basal-like breast cancer. (A) Scale independence and mean connectivity. (B) Gene dendrogram. (C) Trait modules. (D) Module membership versus gene significance in the turquoise module.

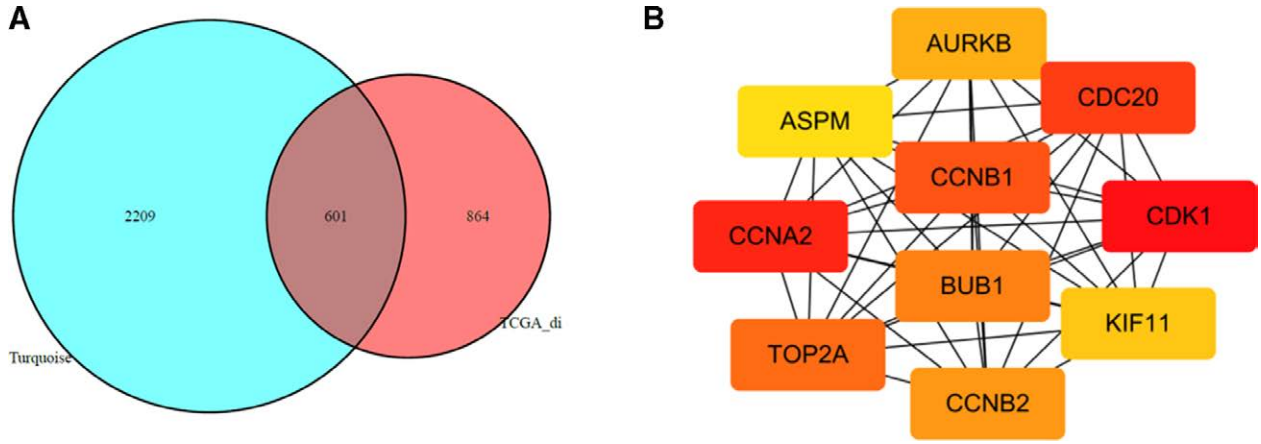


**Figure 3.** The intersected genes and hub gene selection. (A) Venn diagram of genes. (B) Hub genes.

**Table 1**

**The functional analysis of the intersected genes in early stage of basal-like breast cancer.**

| Category | Term | Count | % | *P* value |
|---|---|---|---|---|
| BP | GO:0051301~cell division | 65 | 11.16838 | 3.48E-30 |
| | GO:0007067~mitotic nuclear division | 48 | 8.247423 | 4.53E-23 |
| | GO:0000082~G1/S transition of mitotic cell cycle | 28 | 4.810997 | 1.19E-17 |
| | GO:0006260~DNA replication | 32 | 5.498282 | 2.57E-16 |
| | GO:0007062~sister chromatid cohesion | 25 | 4.295533 | 1.93E-14 |
| | GO:0007059~chromosome segregation | 20 | 3.436426 | 3.00E-13 |
| | GO:0008283~cell proliferation | 42 | 7.216495 | 4.71E-12 |
| | GO:0000070~mitotic sister chromatid segregation | 12 | 2.061856 | 1.15E-10 |
| | GO:0006270~DNA replication initiation | 13 | 2.233677 | 1.55E-10 |
| CC | GO:0005654~nucleoplasm | 179 | 30.75601 | 1.46E-23 |
| | GO:0005829~cytosol | 187 | 32.13058 | 2.44E-18 |
| | GO:0005634~nucleus | 255 | 43.81443 | 1.99E-15 |
| | GO:0000775~chromosome, centromeric region | 19 | 3.264605 | 4.79E-14 |
| | GO:0030496~midbody | 25 | 4.295533 | 1.17E-12 |
| | GO:0000777~condensed chromosome kinetochore | 20 | 3.436426 | 1.40E-11 |
| | GO:0005819~spindle | 22 | 3.780069 | 1.20E-10 |
| | GO:0000922~spindle pole | 20 | 3.436426 | 8.53E-10 |
| | GO:0005737~cytoplasm | 227 | 39.00344 | 1.30E-09 |
| MF | GO:0005515~protein binding | 383 | 65.80756 | 1.72E-19 |
| | GO:0005524~ATP binding | 86 | 14.77663 | 1.20E-07 |
| | GO:0044822~poly(A) RNA binding | 70 | 12.02749 | 1.58E-07 |
| | GO:0008017~microtubule binding | 24 | 4.123711 | 2.45E-07 |
| | GO:0003682~chromatin binding | 33 | 5.670103 | 1.27E-06 |
| | GO:0019901~protein kinase binding | 30 | 5.154639 | 1.25E-05 |
| | GO:0042393~histone binding | 15 | 2.57732 | 3.64E-05 |
| | GO:0042802~identical protein binding | 46 | 7.90378 | 3.90E-05 |
| | GO:0042803~protein homodimerization activity | 44 | 7.560137 | 9.25E-05 |
| | GO:0046978~TAP1 binding | 4 | 0.687285 | 1.28E-04 |
| KEGG | hsa04110: Cell cycle | 37 | 6.357388 | 3.35E-22 |
| | hsa03030: DNA replication | 11 | 1.890034 | 8.37E-07 |
| | hsa05166: HTLV-I infection | 26 | 4.467354 | 2.19E-05 |
| | hsa04114: Oocyte meiosis | 14 | 2.405498 | 4.18E-04 |
| | hsa05203: Viral carcinogenesis | 20 | 3.436426 | 4.71E-04 |
| | hsa05200: Pathways in cancer | 26 | 4.467354 | .012708 |
| | hsa04914: Progesterone-mediated oocyte maturation | 11 | 1.890034 | .002208 |
| | hsa05168: Herpes simplex infection | 17 | 2.920962 | .002399 |
| | hsa04115: p53 signaling pathway | 8 | 1.37457 | .01634 |

BP = biological process, CC = cellule components, MF = molecular function, KEGG = Kyoto Encyclopedia of Genes and Genomes.

### *3.4. Overall survival analysis of hub genes and validation*

The prognostic effect of the above hub genes in early basal-like BC was explored by applying TCGA clinical data. The overall survival analysis revealed that only AURKB was significant (*P* value = .029) (Fig. 5). The TIMER dataset demonstrated that, compared to that in normal breast tissues, the expression level of AURKB was higher in all BC subtypes, with the highest expression in basal-like BC (Fig. 6A). The immune cell infiltration analysis showed that, in basal-like BC tissue, the numbers of infiltrating CD4 + T cells (Rho = 0.162, *P* value = .0322) and naïve CD8 + T cells (Rho = 0.163, *P* value = .0314) were positively correlated with the AURKB expression level, while the numbers of infiltrating naïve B cells (Rho = –0.159, *P*

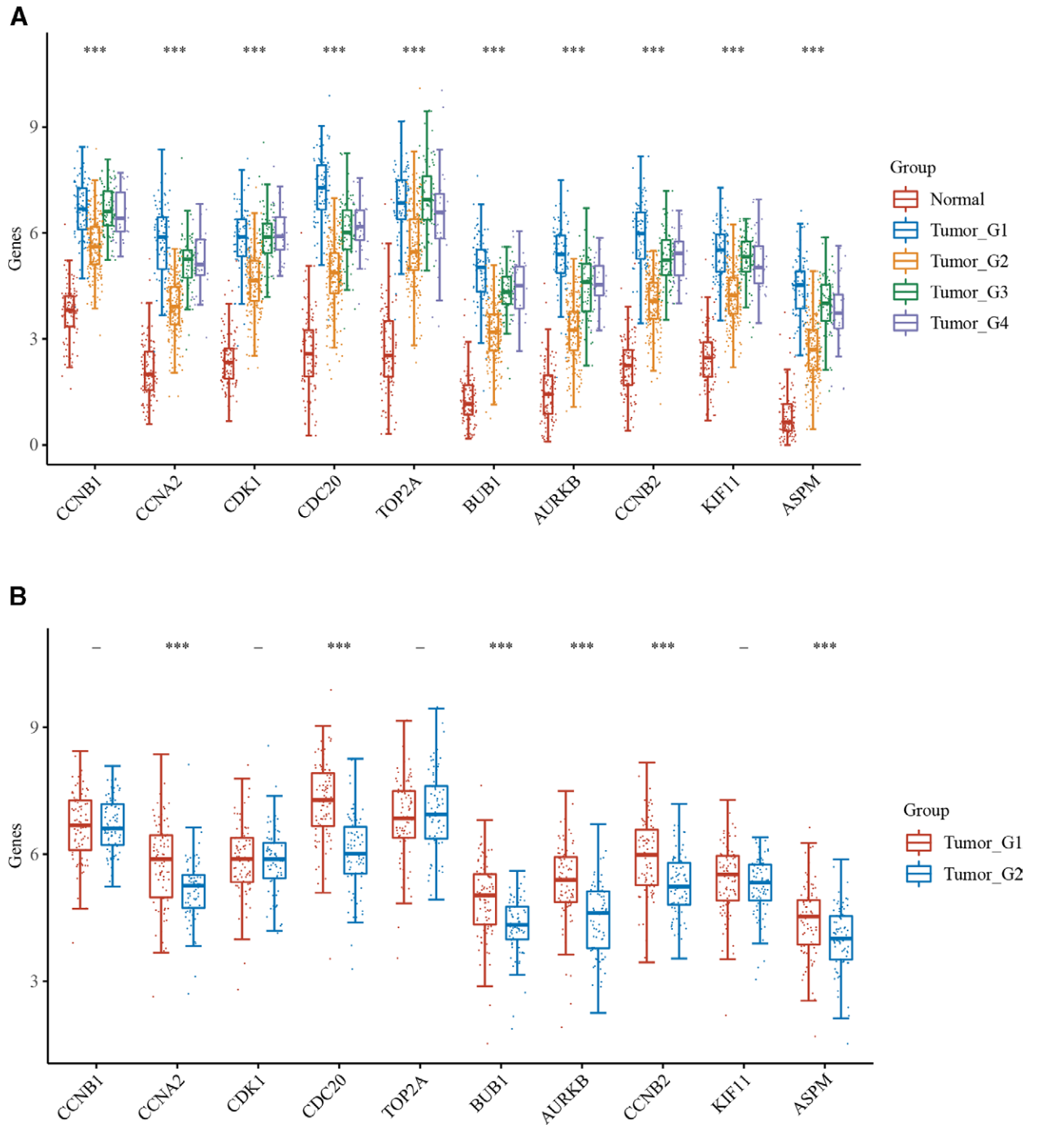


**Figure 4.** Specificity analysis of the 10 hub genes among BC subtypes at an early stage. (A) Analysis between normal tissue and BC subtypes, G1, basal-like, G2, luminal A, G3, luminal B, G4, HER-2 enriched. (B) Analysis between basal-like BC and luminal B BC, G1, basal-like BC, G2, luminal B. *$P < .05$, **$P < .01$, ***$P < .001$. BC = breast cancer.

value = .0362) and macrophage M2 cells (Rho = –0.191, *P* value = .0116) were negatively correlated with the AURKB expression level (Fig. 6B–E).

## 4. Discussion

Although the 5-year survival rate of BC has exceeded 80%, that of basal-like BC is far lower, which is the worst type of BC and accounts for 15% of BC.[13] Basal-like BC represents a group based on the PAM50 classification showing extremely low expression rates of hormone receptors and HER-2 as well as CK5/6 expression.[14] To a certain extent, it intersects with another concept, triple-negative breast cancer. Reports have shown a higher risk of recurrence and metastasis in basal-like BC in the first few years of diagnosis than in other types. Nevertheless, early intervention applied to basal-like BC could result in meaningful impacts on the prognosis of basal-like BC.[15–17]

With the advancement of precision medicine, targeted drugs have gradually emerged, which are commonly used in malignant breast tumors. For example, BRCA1 mutations are more common in breast tumors.[17] As a result, studies on poly ADP-ribose polymerase inhibitors were continuously carried out, and the medicine was eventually approved by the Food and Drug

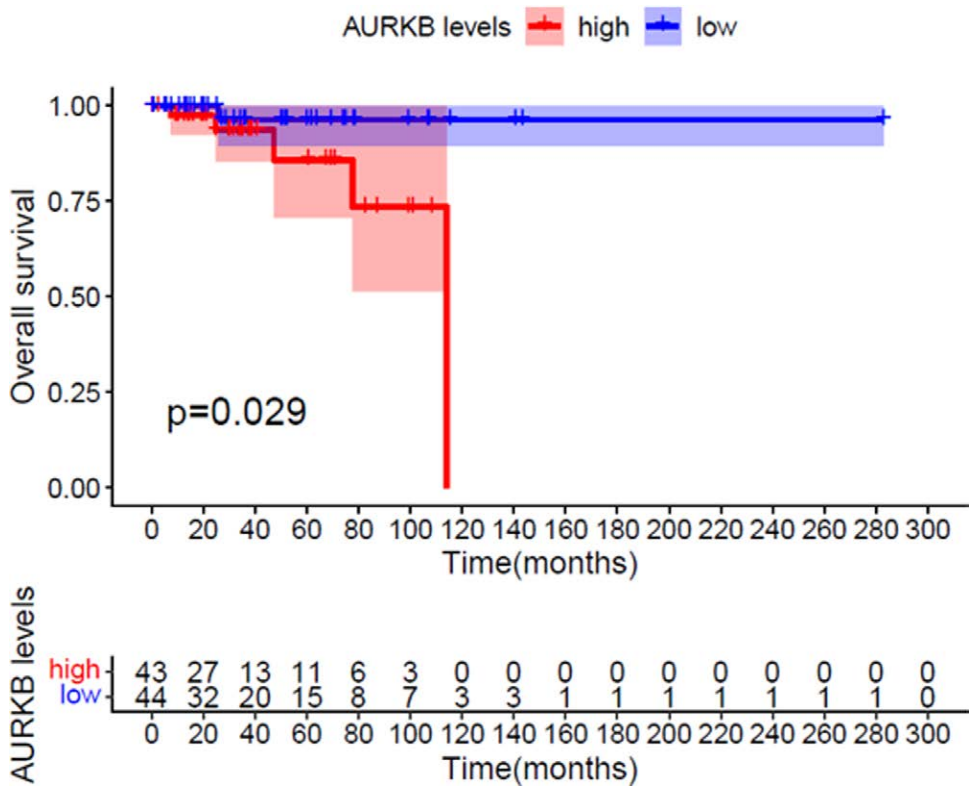


**Figure 5.** Overall survival analysis of AURKB in early-stage basal-like breast cancer. AURKB = aurora kinase B.

Administration and guidelines.[18] However, there is a lack of effective targeted drugs for basal-like BC. Therefore, it is important to find markers that can be related to the prognosis of early breast cancer at the genetic level and explore novel treatment targets.

We screened the gene expression data of early basal-like BC in the TCGA database and identified 1465 DEGs. Then, the WGCNA method was used to explore differences in gene expression between the early basal-like BC tissue and the normal control tissue. After taking the intersection with the DEGs, 601 IGs were obtained that were mostly related to the process of cell division and proliferation. Then, we identified the top 10 hub genes, namely, cyclin B1, CCNA2, cyclin-dependent kinase 1, CDC20, DNA topoisomerase II alpha, BUB1, AURKB, CCNB2, kinesin family member 11, and ASPM. However, only AURKB was found to be associated with overall survival in early basal-like BC. Moreover, we found that the expression level of AURKB was related to the infiltration state of immune cells in the basal-like BC microenvironment.

AURKB, a serine/threonine kinase, is located at 17p13.1. It belongs to the same family together with AURKA and AURKC. AURKB participates in the regulation of cell mitosis, including the regulation of spindle function and the aggregation and separation of chromosomes. Because of its unstable position at the chromosome, abnormal expression is frequently observed. AURKB was reported to be overexpressed and amplified in various types of malignant tumor tissue. The overexpression of AURKB might result in the low expression of proapoptotic proteins and promote cell proliferation.[19] A series of studies in osteosarcoma showed that AURKB might activate intracellular signaling pathways and lead to disease progression.[20] Furthermore, the high expression of AURKB was found to be associated with poor prognosis in renal clear cell carcinoma.[21] Similar results also appeared in gastric cancer and colorectal cancer.[21–23] In addition, in non-small cell lung cancer, Ahmed proved that AURKB was associated with prognosis and also discovered an inverse correlation between the expression of AURKB mRNA and cancer drug resistance.[24]

In breast cancer, researchers have applied immunohistochemical methods to explore the association between AURKB and clinicopathological parameters. AURKB was also reported to be related to chemotherapy resistance in patients undergoing neoadjuvant chemotherapy.[25] In addition, a study revealed that the single-nucleotide polymorphisms in AURKB are related to tumor risk and survival in triple-negative breast cancer,[26] which was consistent with this study. Similarly, the same family gene, AURKA, has been found to be overexpressed and identified as a switch gene in all BC subtypes.[27] However, contrary to this study, the above analyses focused on all BC subtypes or stages, not the early stage. Basal-like BC is characterized by high mortality and earlier recurrence and metastasis.[15] It is particularly important to intervene and evaluate basal-like BC in the early stage.[28] Although AURKB was also found to be overexpressed in all BC subtypes, its expression was highest in basal-like BC. Thus, in this study, we focused on investigating AURKB in early-stage basal-like BC.

## 5. Conclusions

Although we confirmed a relationship between AURKB and the prognosis of early basal-like BC through the TCGA database, the detailed and precise molecular biological mechanism still needs to be verified.

## Author contributions

**Conceptualization:** Yanping Li.
**Data curation:** Keyu Yuan.
**Formal analysis:** Min Wu, Yanping Li.
**Investigation:** Yanping Li.
**Methodology:** Keyu Yuan.
**Project administration:** Shuzhen Lyu.

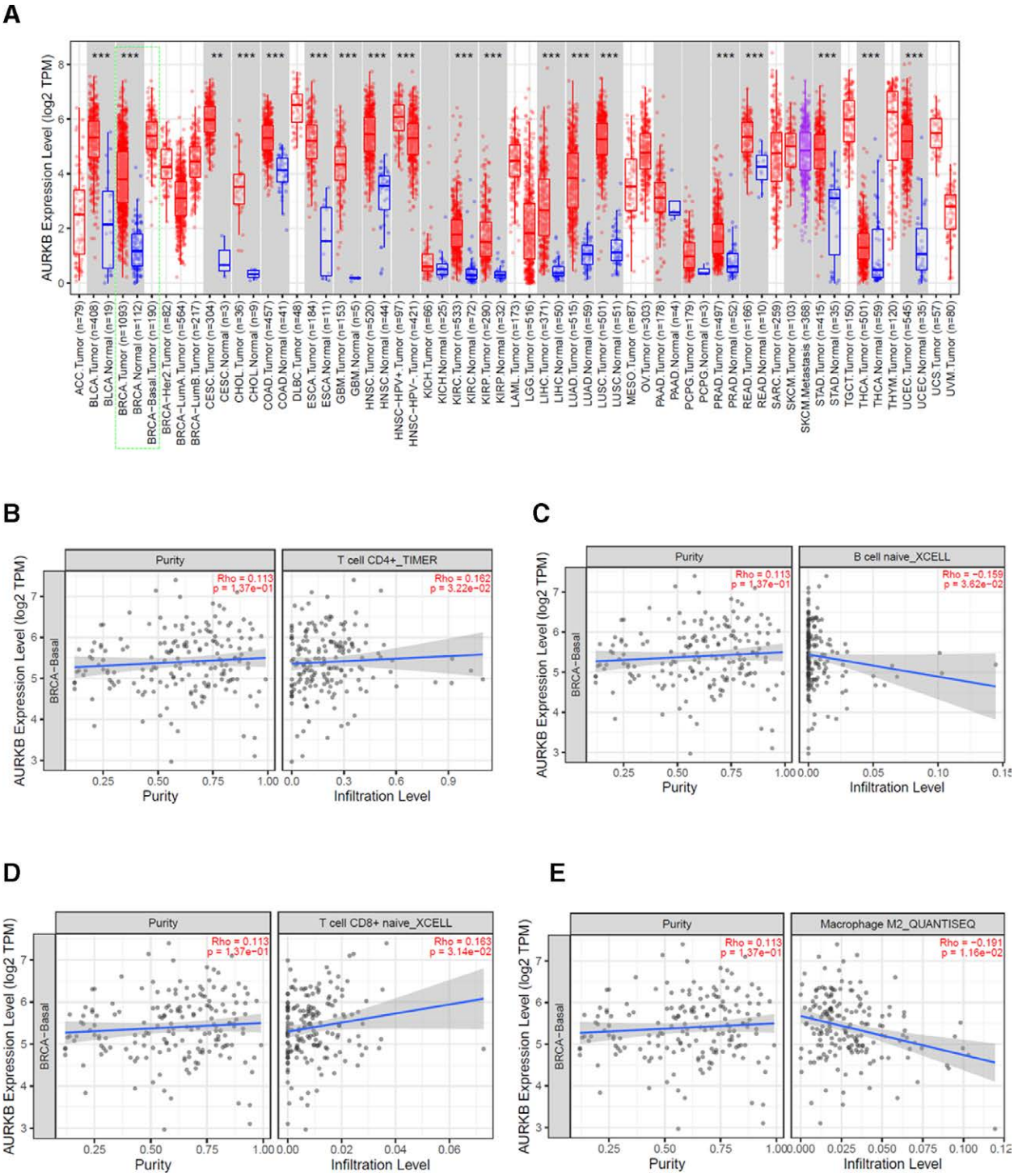


**Figure 6.** The expression of AURKB in cancers and immune cell infiltration analysis of AURKB in BLBC. (A) AURKB expression in various types of cancers. BRCA, breast cancer. (B) CD4 + T cells. (C) Naïve CD8 + T cells. (D) Naïve B cells. (E) M2 macrophages. AURKB = aurora kinase B, BLBC = basal-like breast cancer.

**Resources:** Min Wu.
**Writing – original draft:** Shuzhen Lyu.

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