Performing Data Mining to Explain the Correlation between the BIRC5 Gene and Prognosis in Breast Cancer Patients

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Research

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Abstract

Background: Breast cancer is the most commonly malignant cancers in women, and BIRC5 has been found to be overexpressed in a variety of human tumors. Its expression is associated with the prognosis of many cancers. However, whether BIRC5 mRNA could be used as an independent prognostic factor for breast cancer remains inconsistent in previous studies.

Methods: Altered BIRC5 expression in normal tissue relative to various tumor tissue and in breast cancer patients with different molecular subtypes, clinical outcomes and chemotherapy responses were examined using the Oncomine, GOBO and Kaplan-Meier plotter datasets.

Results: We found that many breast cancers had increased BIRC5 mRNA expression, and GOBO analysis showed that triple-negative cell lines displayed highest BIRC5 mRNA expression levels in the breast cancer cell line panel. Moreover, BIRC5 high mRNA expression was significantly associated with longer relapse-free survival (RFS) in all breast cancer patients. In particular, sub analysis revealed that high mRNA expression of BIRC5 was significantly associated with better survival in ER positive (HR = 2.05, p = 1e-16), but not in ER negative breast cancer (HR = 1.24, p = 0.1), furthermore, the results also demonstrated that BIRC5 high expression was significantly associated with longer RFS in luminal A (HR = 1.51, p = 3.1e-06) and luminal B (HR = 1.28, p = 0.026).

Conclusions: In conclusion, BIRC5 is involved in the development and progression of breast cancer and may be a suitable prognostic marker for human breast cancer.

1. Background

Breast cancer is the most common diagnosed malignancies and the leading cause of cancer death among women worldwide.[1, 2] The hazard and developing trend of breast cancer is closely related to age, lifestyle, economic development and environmental change, and the mortality of breast cancer in Chinese female shows a gradual upward trend in recent years[3]. Surgical therapy is currently the main treatment for breast cancer, other therapies including hormonal therapy, chemotherapy, radiotherapy and molecular targeted therapy. Many molecular targets have been identified in breast cancer. Trastuzumab and lapatinib target the human epidermal growth factor receptor-2 (HER2) receptor and are approved for the treatment of breast cancer. In addition, the expression abnormality of relative genes has been proved to be involved in the incidence of breast cancer and may cause the proliferation, invasion, recurrence and metastasis of tumors[4, 5]. Researches in genetic expression level of breast cancer can provide a theoretical basis for breast cancer prevention, diagnosis, therapy and prognosis[6].

BIRC5 belongs to IAP (the inhibitor of apoptosis) gene family, which not only negatively interferes with apoptosis by directly[7] or indirectly[8] inhibiting caspases activity but also regulates the G2/M phase of the cell cycle by associating with mitotic spindle microtubules[9]. Recently, BIRC5 has been found to be overexpressed in a variety of human tumors, such as breast cancer[10, 11], lung cancer[12], hepatocellular carcinoma[13], bladder cancer[14], colorectal cancer[15, 16] and prostate cancer[17]. By

now, a great majority of studies[18–20] have shown that BIRC5 was a pejorative prognostic marker in breast cancer, but the prognostic value of BIRC5 expression in breast cancer remains controversial. Kennedy SM et al[21] found that high level of nuclear BIRC5 was closely related to prolonged survival time to relapse or death. Other researchers[22, 23] also showed that BIRC5 might have a primarily nuclear cellular location in some tumours and its nuclear expression may be related to a better outcome. Therefore, it is of great importance to explore the relation between the expression of BIRC5 in breast cancer and patients' survival.

2. Methods

2.1 Oncomine analysis

The mRNA levels of distinct GATA family members in different type of cancers were determined through analysis in ONCOMINE database (www.oncomine.org), which is a publicly accessible online cancer microarray database to facilitate discovery from genome-wide expression analyses. In this study, students't-test was used to generate a p-value for comparison between cancer specimens and normal control datasets. The fold change was defined as 2 and p value was set up at 0.01. Significant correlations can be found in an array of BC researches, as showed in typical figures.

2.2 GOBO analysis

Gene expression-based outcome for Breast Cancer Online (GOBO) tool was used for prognostic validation of sets of genes in a pooled breast cancer data set comprising 1881-samples and a 51-sample breast cancer cell line set. The transcription levels of BIRC5 were analyzed by uploading corresponding affymetrix probes to GOBO database (http://co.bmc.lu.se/gobo/gsa.pl)[24]. The calculated P values were adjusted for multiple testing by applying a False Discovery Rate adjustment (FDR = 0.2). P values less than 0.05 were considered statistically significant.

2.3 The Kaplan-Meier plotter survival analysis

Prognostic values of featured GATA members that found specifically high expressed in BC samples were further assessed by displaying the relapse-free survival (RFS) using the Kaplan-Meier plotter (http://kmplot.com/analysis/)[25]. Kaplan–Meier survival curve, log-rank P value and HR with 95% confidence intervals were calculated and plotted in R using Bioconductor packages.

3. Results

3.1 BIRC5 expression is overexpressed in breast cancer

To explore the expression of BIRC5 transcript in breast cancer and normal tissues, we used the Oncomine tool to analyze several published microarray gene expression studies. Our analysis revealed a strong increase in BIRC5 mRNA expression in breast cancer tissues as compared to normal tissues. BIRC5 transcripts were 7.711 fold elevated in breast cancer samples as compared with normal tissues in a

dataset with 593 samples that derived from the Cancer Genome Atlas database (p = 5.49E-31) (Fig. 1A). In another dataset from Curtis, BIRC5 was 2.677 fold elevated in breast cancer samples as compared with normal tissues (p = 6.78E-7) (Fig. 1B).

Figure 1 depicts the meta-analysis of BIRC5 transcripts across nine breast cancer datasets and the median rank of BIRC5 is 213 (p-value = 1.66E-9, Fig. 2).

3.2 BIRC5 expression in different molecular subtypes of breast cancer cell lines (GSA-Cell line)

To investigated BIRC5 mRNA expression levels across the breast cancer cell line panel, we used GSA-Cell line application of GOBO tool. Highest gene expression was observed in the basal B subgroup associated with a more stem-cell like phenotype and recently also the claudin-low subtype[26], followed by the basal A and luminal subgroups as defined by Neve et al[26] (Fig. 3A). In line with previous reports analyzing BIRC5 protein expression we found that triple-negative cell lines displayed highest BIRC5 mRNA expression levels (Fig. 3B).

3.3 Effect of level of BIRC5 expression on patients' survival

To investigate the prognostic value of mRNA level of BIRC5 in breast cancer, we used the the Kaplan-Meier plotter to analyze relapse-free survival (RFS) of various molecular subtypes with different BIRC5 transcript level. In Fig. 4, BIRC5 high mRNA expression was significantly associated with longer RFS in all breast cancer patients. In particular, sub analysis revealed that high mRNA expression of BIRC5 was significantly associated with better survival in ER positive (HR = 2.05, p = 1e-16, Fig. 4G), but not in ER negative breast cancer (HR = 1.24, p = 0.1) (Fig. 4A and 4B), furthermore, the results also demonstrated that BIRC5 high expression was significantly associated with longer RFS in luminal A (HR = 1.51, p = 3.1e-06, Fig. 4E), luminal B (HR = 1.28, p = 0.026, Fig. 4F).

4. Discussion

While an increasing number of target genes have been discovered and mortality by breast cancer is decreasing in recent years, breast cancer is still the second most common cause of cancer death in women[27]. Thus, it is important to identify more biomarkers that will contribute to improving the prognosis of breast cancer patients. We conducted this analysis to evaluate the prognostic value of BIRC5 expression in breast cancer.

According to the presence of HER2, ESR1 and KI67, breast cancer can be classified into four molecular subtypes: basal-like/triple negative (TN), luminal A, luminal B and HER2+. Our analysis showed a strong increase in BIRC5 mRNA expression in breast cancer tissues as compared to normal tissues (Fig. 1). BIRC5 was found to be expressed in fetal tissues and most human cancers, but absent in normal and differentiated tissues[28]. Its high expression in the primary cancer tend to associate with a poor

prognosis for the patients[10, 20, 29]. However, the relation between high expression of BIRC5 and the prognosis of breast cancer is ambiguous, because other studies have reported it to be either irrelevant[30] or good prognosis[21].

Our study found BIRC5 to be a positive prognostic factor in all patients with breast cancer (P = 9.4E-12, Fig. 4G), particularly among ER positive cases. Moreover, we discovered that high level of BIRC5 in luminal A or B subtypes showed prolonged RFS (Fig. 4E, 4F). Ito T et al[22] reported that BIRC5 was mainly located in the nucleus of human hepatocellular carcinoma. Then Okada E et al[23] found that BIRC5 was present in both nucleus and cytoplasm of gastric cancer cells, but a nuclear localization may play an important physiological role in hindering tumor progression. Furthermore, Kennedy SM et al[21] revealed that BIRC5 may be predominantly in the nucleus in breast carcinoma and the nuclear expression of BIRC5 to be an independent prognostic factor of good prognosis. Therefore, we inferred that BIRC5 may have a main location in the nucleus in luminal A or B subtypes of breast cancer.

On the contrary, BIRC5 was a negative prognostic factor in HER2 + subtype (Fig. 4C). Kim JS et al[31] found that the HR-/HER2 + subtype of breast cancer is resistant to radiotherapy and the radio-resistance was mediated by HER2-STAT3-BIRC5 signaling. This suggested that BIRC5 might be a promising target in HER2 + breast cancer.

To date, basal-like subtype was considered to be of poorer prognosis[32, 33]. Interestingly, we found that the expression of BIRC5 in basal-B was significantly higher than basal-A or luminal-like subtypes of breast cancer (Fig. 3A). Similarly, the level of BIRC5 in triple negative breast cancer (TNBC) was higher than HER2 + and HR + subtypes (Fig. 3B). Our analysis revealed that high level of BIRC5 seemed to a negative factor for the prognosis of TNBC, but there were no significant statistic difference with P = 0.22 (Fig. 4D). This result may be due to insufficient cases of TNBC in all patients with breast cancer. Likewise, Zhang C[34] and his colleages reported that BIRC5 were ≥ 2-fold higher in TNBC compared to NTNBC (non-TNBC) and healthy individuals and its high expression were related to poor survival.

5. Conclusions

In conclusion, our analysis showed that BIRC5 was a positive prognostic factor for luminal A or B subtypes of breast cancer and a negative prognostic indicator for HER2 + breast cancer. Further studies need to be carried out to confirm the relation between BIRC5 and basal like breast cancer.

Abbreviations

HER2: Human epidermal growth factor receptor-2; GOBO: Gene expression-based outcome for Breast Cancer Online; RFS: Relapse-Free Survival; TN: Triple Negative.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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There are no financial/commercial conflicts of interest involving any of the authors of this study.

Authors' contributions

Dongsheng Hong had the original idea for this article. Jing Chen and Yanfang Zhang contributed to the study design and paper writing. Ziqi Ye and Xiaoyang Lu reviewed previous studies. All authors read and approved the final version of the article.

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Figures

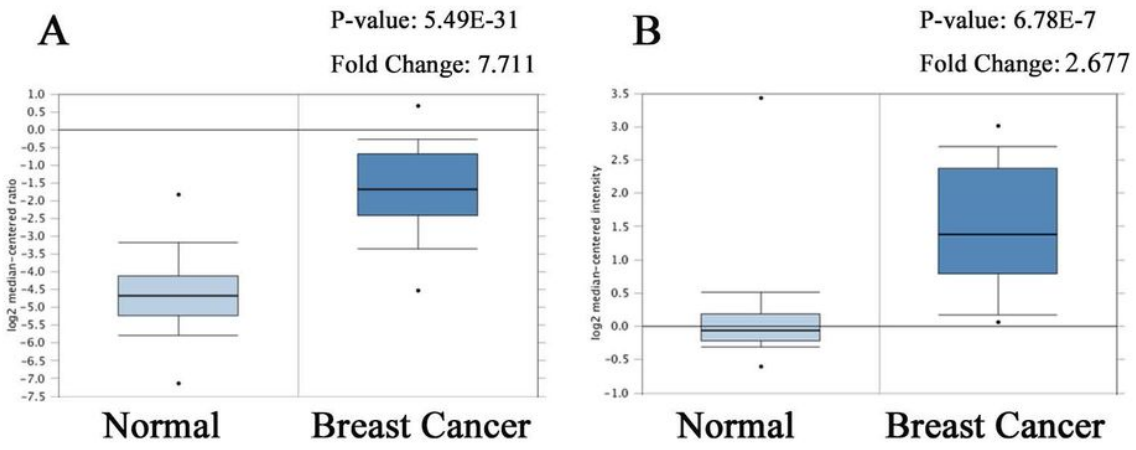

Figure 1

Figure 1

Gene Expression-Based Outcome for Oncomine analyses of BIRC5 of breast cancer. (A) Data from the Cancer Genome Atlas database; (B) Data from Curtis database.

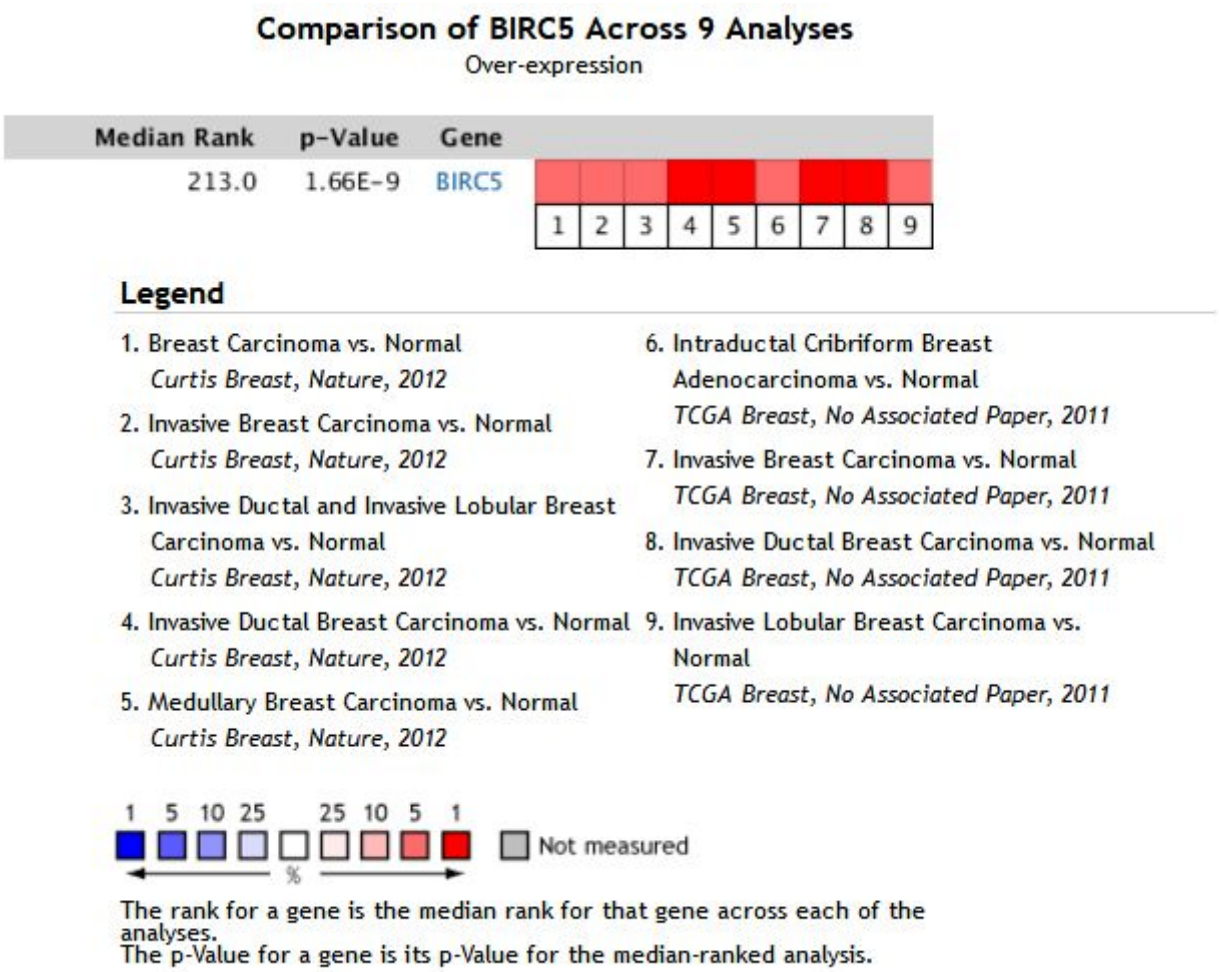

Figure 2

Meta-analysis of BIRC5 transcripts across nine breast cancer datasets.

Figure 3

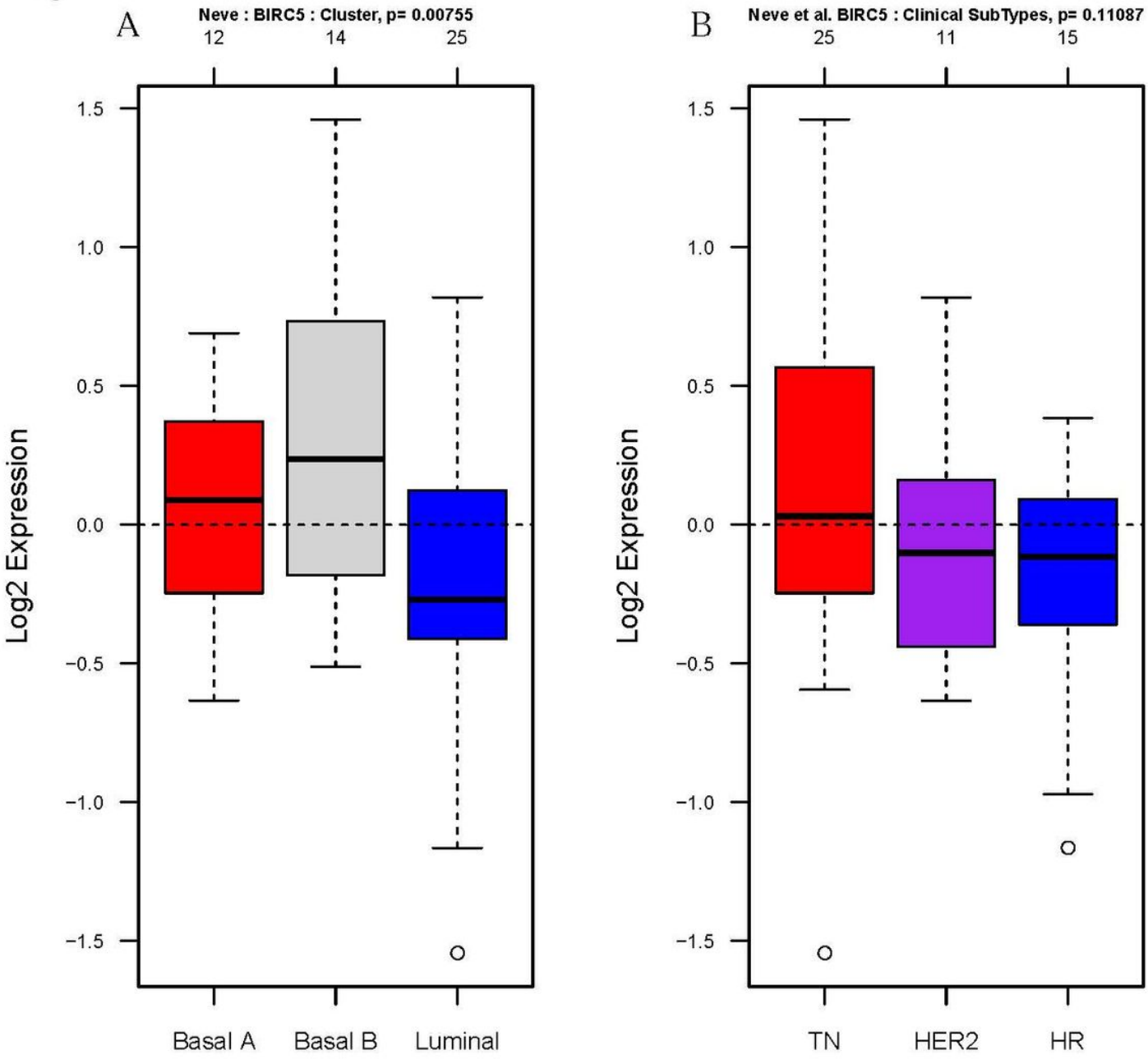

Figure 3

Gene Expression-Based Outcome for Breast Cancer Online algorithm (GOBO) analyses of BIRC5 transcript among subtypes of breast cancer.

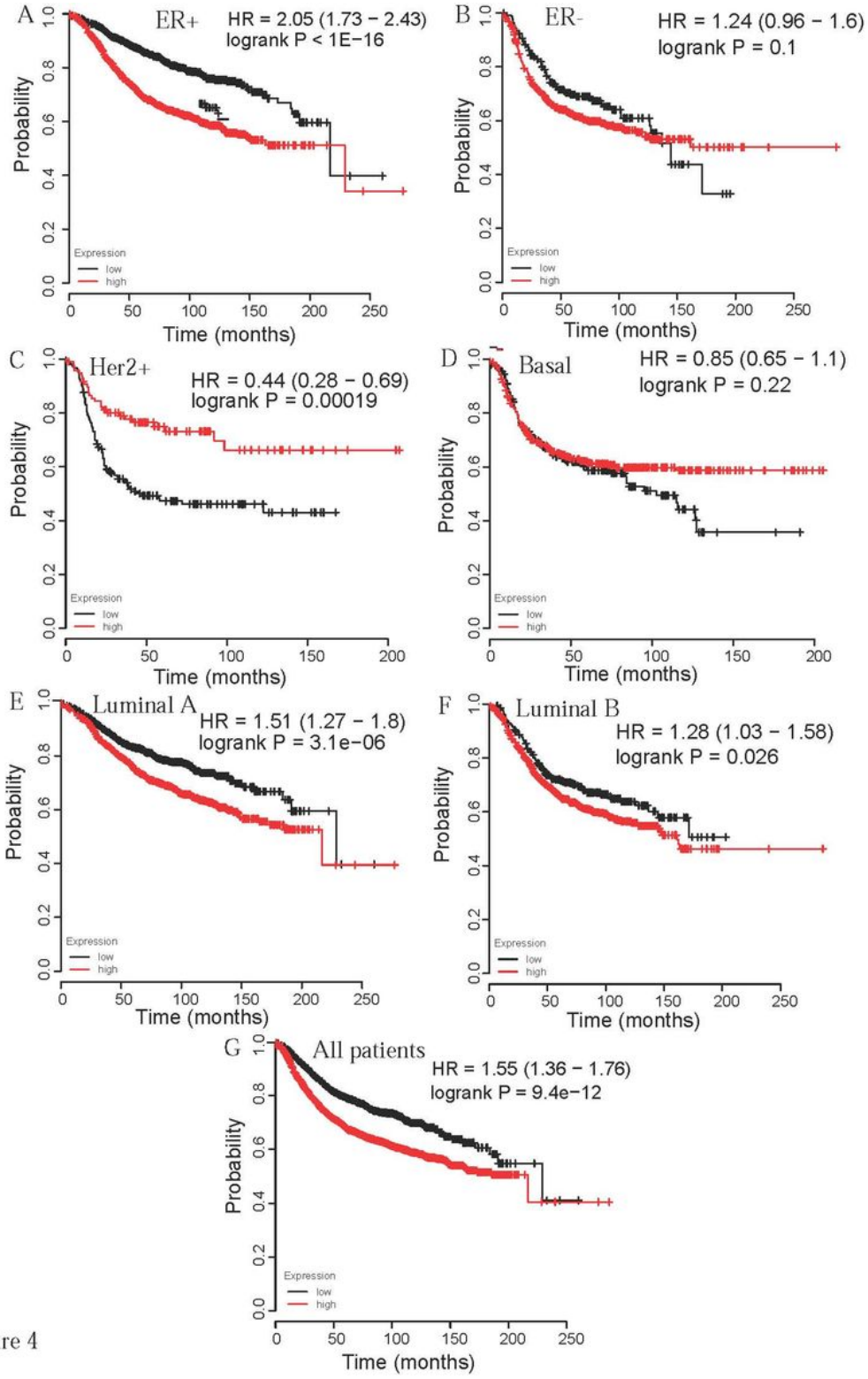

Figure 4

Figure 4

The prognostic values of BIRC5 transcripts in breast cancer patients. (A) High mRNA expression of BIRC5 was significantly associated with better RFS in ER positive breast cancer patients; (B) High mRNA expression of BIRC5 was not significantly associated with better RFS in ER negative breast cancer patients; (C) High mRNA expression of BIRC5 was not significantly associated with better RFS in Her2 positive breast cancer patients; (D) High mRNA expression of BIRC5 was not significantly associated with

better RFS in basal subtype breast cancer patients; (E) High mRNA expression of BIRC5 was significantly associated with better RFS in luminal A subtype breast cancer patients; (F) High mRNA expression of BIRC5 was significantly associated with better RFS in luminal B subtype breast cancer patients; (G) High mRNA expression of BIRC5 was significantly associated with better RFS in all breast cancer patients.