Aims: Baculoviral inhibitor of apoptosis repeat containing 5 (BIRC5) plays vital roles in carcinogenesis by influencing cell division and proliferation and by inhibiting apoptosis. However, the prognostic significance of BIRC5 remains unclear in breast cancer.

Methods: BIRC5 expression and methylation status were evaluated using the Oncomine and The Cancer Genome Atlas (TCGA) databases. The relevance between BIRC5 and different clinicopathological features as well as survival information was analyzed using the bc-GenExMiner database and Kaplan–Meier Plotter. BIRC5–drug interaction network was obtained using the Comparative Toxicogenomics Database.

Results: Based on the results from databases and own hospital data, BIRC5 was higher expressed in different breast cancer subtypes compared with the matched normal individuals. Hormone receptors were negatively correlated with BIRC5 expression, whereas the Scarff–Bloom–Richardson (SBR) grade, Nottingham Prognostic Index (NPI), human epidermal growth factor receptor-2 (HER-2) status, basal-like status, and triple-negative status were positively related to BIRC5 level in breast cancer samples with respect to normal tissues. High BIRC5 expression was responsible for shorter relapse-free survival, worse overall survival, reduced distant metastasis free survival, and increased risk of metastatic relapse event. BIRC5–drug interaction network indicated that several common drugs could modulate BIRC5 expression. Furthermore, a positive correlation between BIRC5 and cell-division cycle protein 20 (CDC20) gene was confirmed.

Conclusion: BIRC5 may be adopted as a promising predictive marker and potential therapeutic target in breast cancer. Further large-scale studies are needed to more precisely confirm the value of BIRC5 in treatment of breast cancer.

Introduction
Breast cancer is now the most common malignancy among women worldwide [1,2]. Although precise surgery and adjuvant systemic treatments including chemotherapeutic agents, radiotherapy, hormone therapy, and molecular targeting drugs greatly improve the overall outcome, the prognosis of breast cancer remains poor. The limitation of clinical, pathological, and molecular features in individualized tumor therapy urgently requires a novel approach to predict outcome and treatment response. Therefore, finding some more available and effective markers as surrogates of these features is of crucial importance [3].

As a mitotic spindle checkpoint gene, baculoviral inhibitor of apoptosis repeat containing 5 (BIRC5, also known as survivin) has been shown to play vital roles in carcinogenesis by influencing cell division and proliferation and by inhibiting apoptosis [4]. Since BIRC5 is frequently overexpressed in a majority of...
malignancies [5–7], treatment that targets BIRC5 has been increasingly noticed as a novel strategy for various malignant tumors. For example, inactivation of nuclear export signal for BIRC5 may increase therapy response in head and neck cancer patients [8]. Both molecular suppression by gene editing approach and pharmacological inhibition by BIRC5 antagonist could reduce the growth, migration, and invasiveness of ovarian cancer cells [7]. In terms of breast cancer, BIRC5 was highly expressed in triple-negative subtype and BIRC5 repression was able to decrease the proliferation of breast cancer cells, implying that BIRC5 acts like a tumor driver [9]. Moreover, it was demonstrated that BIRC5 was a pejorative marker in stage II/III breast cancer with no response to neoadjuvant chemotherapy [10]. Besides, BIRC5 expression has been found to confer resistance to chemotherapy and radiation. Targeting BIRC5 in experimental models improves survival [11]. Together, these findings indicate that BIRC5 may not only function as an oncogene, but also as a promising predictive biomarker and potential therapeutic target in cancer [12]. Therefore, the present work was carried out to validate the expression pattern, potential function, prognostic value, and drug interaction network of BIRC5 in breast cancer by performing bioinformatics analysis of several large online databases.

**Materials and methods**

**Breast tissue samples**

A total of 18 pairs of breast tissue samples were obtained from the Affiliated Changzhou No.2 People’s Hospital of Nanjing Medical University between 2014 and 2016. The collection and use of samples was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Changzhou No.2 People’s Hospital [13]. Informed written consent was received from all patients.

**Oncomine**

The Oncomine (http://www.oncomine.org), a database containing publicly available microarray data on multiple tumors, was searched to check the level of BIRC5 in breast cancer and normal tissues with the options as follows: fold change ≥ 2, P-value ≤ 1E-4, and the top 10% gene ranking [14]. BIRC5 co-expression profile was shown in the heatmap.

**Ualcan**

The Ualcan (http://ualcan.path.uab.edu/), a popular web source for in-depth analysis of The Cancer Genome Atlas (TCGA) data, was used to validate the relative level of BIRC5 across tumor and normal samples, as well as in tumor subgroups according to different stages [15]. Besides, the promoter methylation level of BIRC5 in breast cancer and normal tissues was obtained by using Ualcan.

**bc-GenExMiner**

The Breast Cancer Gene-Expression Miner v4.1 (bc-GenExMiner v4.1, http://bcgenex.centregauducheau.fr/BC-GEM), an open access database of published annotated genomics data, was utilized to analyze the relevance between BIRC5 and specific clinicopathological features of breast cancer [16,17]. Association between BIRC5 and metastatic relapse event was assessed using the prognostic module, and correlation of BIRC5 and co-expressed cell-division cycle protein 20 (CDC20) was evaluated using the correlation module.

**UCSC Xena**

The UCSC Xena browser (http://xena.ucsc.edu/) was used to analyze the TCGA Breast Cancer data using the level 3 data. The heatmap and correlation between BIRC5 and CDC20 were then constructed.

**Kaplan–Meier Plotter**

The Kaplan–Meier Plotter (http://kmplot.com/analysis/), a web tool capable to check the effect of 54675 genes on survival using 5143 clinical breast cancer samples, was applied to show the prognostic value of BIRC5 in relapse-free survival, overall survival, and distant metastasis-free survival [18]. The hazard ratio (HR) with 95% confidence interval (CI), and log-rank P-value were calculated automatically.
Comparative Toxicogenomics Database
The Comparative Toxicogenomics Database (http://ctdbase.org/) was employed to construct BIRC5–drug interaction network [19]. Concretely, BIRC5 was checked in the database for potential chemical drugs that could decrease/increase the mRNA or protein expression of BIRC5. Drugs were picked based on their clinical applications in breast cancer treatment. BIRC5–drug interaction network was then generated using the Cytoscape (http://cytoscape.org/) [20,21]. BIRC5 gene was also queried in the database and the results were filtered by selecting BIRC5-related pathways.

RNA isolation and real-time PCR and Western blot
Total RNA was extracted using the TRizol reagent (TaKaRa, Japan), and 1000 ng RNA was reverse transcribed into cDNA using the SYBR PrimeScript RT-PCR kit (Takara Bio Inc., Japan) on an iCycler iQ system (Bio-Rad, U.S.A.). Real-time PCR was performed using the same kit on a Light Cycler 480 (Roche, Australia). The primer sequence of BIRC5 and endogenous control β-actin was as follows: forward, 5′-ATCGTCCGGTGGCTTTCC-3′; reverse, 5′-CACGGCCGACTTTCTCGCAG-3′; and forward, 5′-GCTGTGCT ATCCCTGTACGC-3′; reverse, 5′-TGCTCAGGGCAGCGGAACC-3′, respectively. All reactions, including the negative controls, were performed in triplicate.

Tissue proteins were extracted, electrophoresed through SDS/PAGE gel, and transferred to PVDF membranes for Western blot. BIRC5 protein level was quantified using antibody against BIRC5 (1:1000, Santa Cruz, U.S.A.), β-actin (Sigma, Germany) was used for normalization. Bound proteins were visualized by using the ECL Plus Kit (Millipore, U.S.A.) with Image Lab Software (Bio-Rad, U.S.A.).

Statistical analysis
According to protocols of the above tools, mRNA levels of BIRC5 in breast cancer and normal tissues in each individual dataset were analyzed using the Student’s t test. Kaplan–Meier survival analysis was performed to compare patient survival based on BIRC5 expression by log-rank test. Global significant difference between groups of clinical parameters was assessed by Welch’s test, along with Dunnett–Tukey–Kramer’s.

Results
BIRC5 expression and methylation status in breast cancer patients
We first measured the BIRC5 levels in 20 cancer types. Oncomine database revealed that BIRC5 was significantly higher expressed in breast cancer patients compared with the matched normal individuals (Figure 1A). TCGA data analyzed by the Ualcan online tool confirmed that higher BIRC5 was expressed in breast cancer tissues than in normal tissues (Figure 1B, P < 0.05). Moreover, patients with a more advanced stage of breast cancer tended to express higher levels of BIRC5 (Figure 1C.) Consistent with the results from databases, we also compared the BIRC5 expression in breast cancer tissues and adjacent normal tissues in our hospital and found that BIRC5 was elevated in breast cancer tissues both in mRNA level (Figure 1D) and protein level (Figure 1E). Specifically, increased level of BIRC5 was observed in medullary breast carcinoma, invasive ductal breast carcinoma, invasive breast carcinoma, invasive ductal and invasive lobular breast carcinoma, breast carcinoma, invasive lobular breast carcinoma, and intraductal cribriform breast adenocarcinoma with respect to normal tissues (Figure 2A–I). Heatmap and DNA methylation analysis by the Ualcan online tool confirmed that higher BIRC5 was expressed in breast cancer patients compared with the matched normal individuals (Figure 1A). TCGA data also demonstrated strongly higher BIRC5 expression in basal-like and triple-negative breast cancer patients with respect to non-basal-like and non-triple-negative patients (Figure 4H, I and Table 1).

BIRC5 expression and clinicopathological features in breast cancer patients
We checked the relevance of BIRC5 expression and different clinicopathological features by using the bc-GenExMiner web-based tool. No significant difference could be found between ≤51- and >51-year groups (Figure 4A and Table 1). Breast cancer patients with more advanced Scarff–Bloom–Richardson (SBR) grade and Nottingham Prognostic Index (NPI) showed elevated BIRC5 gene [22,23] (Figure 4B,C). Hormone receptor status was found to correlate negatively with BIRC5 (Figure 4D, E and Table 1); whereas human epidermal growth factor receptor-2 (HER-2) status was positively associated with BIRC5 level (Figure 4F and Table 1). In terms of nodal status, no significant difference was found between positive group and negative group (Figure 4G and Table 1). Our results also demonstrated strongly higher BIRC5 expression in basal-like and triple-negative breast cancer patients with respect to non-basal-like and non-triple-negative patients (Figure 4H, I and Table 1).
Figure 1. BIRC5 expression in breast cancer patients

(A) Expression of BIRC5 in 20 types of cancer and the matched normal individuals using the Oncomine database. Red and blue indicate the numbers of datasets with statistically significant (P<0.05) higher expressed and lower expressed BIRC5 gene. (B) Higher mRNA BIRC5 was expressed in breast cancer tissues than in normal tissues (P<0.05) using Ualcan online tool. (C) Patients with a more advanced stage of breast cancer tended to express higher levels of BIRC5 using Ualcan online tool. (D) Expression of BIRC5 in 18 pairs of breast cancer tissues and adjacent normal breast tissues obtained from our own hospital. (E) BIRC5 protein expression in two pairs of breast cancer tissues and adjacent normal breast tissues (*, P<0.05).
Figure 2. Box plot comparing BIRC5 expression in normal tissues and breast cancer patients obtained from the Oncomine database
Analysis is shown for (A) medullary breast carcinoma, (B) invasive ductal breast carcinoma, (C) invasive breast carcinoma, (D) invasive ductal and invasive lobular breast carcinoma, (E) breast carcinoma, (F) invasive breast carcinoma, (G) invasive ductal breast carcinoma, (H) invasive lobular breast carcinoma, and (I) intraductal cribriform breast adenocarcinoma (*, P<0.05).

Figure 3. BIRC5 methylation status in breast cancer patients
(A) Heatmap of BIRC5 expression and DNA methylation status using the TCGA data analyzed by the UCSC Xena browser. (B) Higher promoter methylation level of BIRC5 was observed in breast cancer tissues, with respect to normal tissues.
Figure 4. Box plot evaluating the relevance of BIRC5 expression and different clinicopathological features using the bc-GenExMiner web-based tool.
Analysis is shown for (A) age, (B) SBR, (C) NPI, (D) ER, (E) PR, (F) HER-2, (G) nodal status, (H) basal-like status, and (I) triple-negative status. Abbreviations: ER, estrogen receptor; PR, progesterone receptor (*, P < 0.05).

**BIRC5 expression and prognosis in breast cancer patients**

We then investigated the prognostic value of BIRC5 gene using the Kaplan–Meier Plotter. While breast cancer patients with lower level of BIRC5 showed longer relapse-free survival and better overall survival, patients with increased BIRC5 expression displayed shorter distant metastasis-free survival (Figure 5A–C). By mining previously available data using the bc-GenExMiner, we analyzed the association between BIRC5 and metastatic relapse-free survival. High level of BIRC5 was significantly associated with elevated risk of metastatic relapse event (HR = 1.42, 95% CI: 1.33–1.52, P < 0.0001), as suggested by the forest plot (Figure 5D).

**BIRC5–drug interaction network**

Given that high level of BIRC5 conferred shorter survival in breast cancer patients, we then sought to investigate whether BIRC5 and potential chemical drugs could modulate each other using the Comparative Toxicogenomics Database. BIRC5–drug interaction network indicated that a number of commonly used drugs could modulate the mRNA or protein expression of BIRC5. Specifically, chemotherapy agents including cisplatin, epirubicin, and doxorubicin, endocrine drugs such as tamoxifen and fulvestrant, and molecular targeting drugs lapatinib and palbociclib could decrease BIRC5 level; whereas docetaxel was able to increase BIRC5 expression (Figure 6). By using the
Table 1: Relevance of BIRC5 expression and different clinicopathological features using the bc-GenExMiner database

| Variables                  | Number of patients | BIRC5 mRNA | P-value |
|----------------------------|--------------------|------------|---------|
| Age (years)                |                    |            |         |
| ≤51                        | 1392               | -          | 0.1561  |
| >51                        | 2210               | -          |         |
| ER                         |                    |            |         |
| Negative                   | 1559               | Increased  | <0.0001 |
| Positive                   | 3988               | -          |         |
| PR                         |                    |            |         |
| Negative                   | 946                | Increased  | <0.0001 |
| Positive                   | 1439               | -          |         |
| HER-2                      |                    |            | 0.0152  |
| Negative                   | 1409               | -          |         |
| Positive                   | 201                | Increased  |         |
| Nodal status               |                    |            | 0.2654  |
| Negative                   | 2493               | -          |         |
| Positive                   | 1562               | -          |         |
| Basal-like status          |                    |            | <0.0001 |
| Non-basal-like             | 4200               | -          |         |
| Basal-like                 | 1144               | Increased  |         |
| Triple-negative status     |                    |            | <0.0001 |
| Non-triple-negative        | 4099               | -          |         |
| Triple-negative            | 374                | Increased  |         |

Abbreviation: ER, estrogen receptor; PR, progesterone receptor.

Figure 5. Survival curves derived from the Kaplan–Meier Plotter and forest plot generated from the bc-GenExMiner database evaluating the prognostic significance of BIRC5

Analysis is shown for (A) relapse-free survival, (B) overall survival, (C) distant metastasis-free survival, and (D) metastatic relapse event.
Figure 6. *BIRC5*-drug interaction network obtained from the Comparative Toxicogenomics Database

The network shows that several common drugs could modulate the mRNA or protein expression of *BIRC5*. For example, tamoxifen could decrease *BIRC5* expression (blue), while docetaxel could increase *BIRC5* level (red).

Comparative Toxicogenomics Database, several important *BIRC5*-related signaling pathways were also obtained including apoptosis, cell cycle, immune system, hippo signaling pathway, platinum drug resistance, pathways in cancer, and TP53 regulation (Table 2).

### Table 2 Analysis of *BIRC5*-involved pathway terms

| Pathway ID | Pathway term |
|------------|--------------|
| KEGG: hsa04210 | Apoptosis |
| REACT: R-HSA-1640170 | Cell cycle |
| REACT: R-HSA-69278 | Cell cycle, mitotic |
| REACT: R-HSA-1280215 | Cytokine signaling in immune system |
| REACT: R-HSA-74160 | Gene expression |
| REACT: R-HSA-212436 | Hippo signaling pathway |
| KEGG: hsa04390 | Immune system |
| REACT: R-HSA-168256 | Interleukin-4 and 13 signaling |
| REACT: R-HSA-6785807 | Metabolism of proteins |
| REACT: R-HSA-392499 | Pathways in cancer |
| KEGG: hsa05200 | Platinum drug resistance |
| KEGG: hsa01524 | Post-translational protein modification |
| REACT: R-HSA-494147 | Signaling by interleukins |
| REACT: R-HSA-194315 | Signaling by Rho GTPases |
| REACT: R-HSA-162582 | Signaling transduction |
| REACT: R-HSA-5633008 | TP53 regulates transcription of cell death genes |
| REACT: R-HSA-370989 | Transcriptional regulation by TP53 |
| REACT: R-HSA-6803205 | TP53 regulates transcription of several additional cell death genes whose specific roles in p53-dependent apoptosis remain uncertain |
Figure 7. Co-expression of BIRC5 gene

(A) Co-expression profile of BIRC5 analyzed using the Oncomine database. (B) Correlation between BIRC5 and CDC20 in breast cancer analyzed using the bc-GenExMiner software. (C) Heatmap of BIRC5 and CDC20 expression across PAM50 breast cancer subtypes using the TCGA data analyzed by the UCSC Xena browser. (D) Correlation between BIRC5 and CDC20 expression using the TCGA data analyzed by the UCSC Xena browser.

Co-expression of BIRC5 gene

We finally investigated the co-expression of BIRC5 gene using the Oncomine. BIRC5 co-expression profile consists of a large cluster of 19574 genes from 336 breast cancer samples (Figure 7A). The most highly correlated gene was CDC20. CDC20 is an important regulatory cell cycle protein that activates the anaphase-promoting complex during mitosis, resulting in chromatid separation, and entrance of cell cycle into anaphase [24]. Data mining using the bc-GenExMiner revealed that BIRC5 was positively correlated with CDC20 (Figure 7B). Such positive relationship was verified by analyzing TCGA database using the UCSC Xena (Figure 7C,D).

Discussion

Based on the high activation of BIRC5 during tumorigenesis in various cancer types, treatment that targets BIRC5 has been increasingly noticed as a promising therapeutic strategy [11]. However, the detailed expression pattern, potential function, prognostic value, and drug interaction network of BIRC5 remain largely unclear in breast cancer.

First, our analysis using the Oncomine and TCGA databases revealed that BIRC5 gene was higher expressed in breast cancer patients with respect to normal individuals. Moreover, Oncomine showed that BIRC5 was significantly elevated in medullary breast carcinoma, invasive ductal breast carcinoma, invasive breast carcinoma, invasive ductal and invasive lobular breast carcinoma, breast carcinoma, invasive lobular breast carcinoma, and intraductal cribriform breast adenocarcinoma, compared with the corresponding normal tissues.

Second, we investigated the mechanisms of BIRC5 dysregulation in breast cancer. After checking the DNA methylation status in TCGA, we found that BIRC5 expression was negatively related to DNA methylation and higher promoter methylation level of BIRC5 was expressed in breast cancer tissues. These observations indicated that DNA methylation might be an important mechanism of BIRC5 dysregulation in breast cancer.
Then, we analyzed the relevance of BIRC5 expression and different clinicopathological features. In the current work, estrogen receptor (ER) and progesterone receptor (PR) were negatively correlated with BIRC5 expression. We also confirmed that high BIRC5 level was associated with increased SBR and NPI, HER-2 positivity, basal-like status, and triple-negative status. Since patients with ER or PR negative, HER-2 positive, basal-like or triple-negative status generally display therapy insensitivity and inferior prognosis, our results suggested that lower expression of BIRC5 may predict a satisfied clinical outcome of breast cancer.

Next, we checked the prognostic significance of BIRC5 in breast cancer and demonstrated that high BIRC5 expression was responsible for shorter relapse-free survival, worse overall survival, reduced distant metastasis-free survival, and increased risk of metastatic relapse event. This was based on survival curves obtained from the Kaplan–Meier Plotter and forest plot generated from the bc-GenExMiner database. Thus, our findings provided evidence that BIRC5 could be a useful predictive prognostic marker for breast cancer. Indeed, several studies have reported BIRC5 as a prognostic marker in breast cancer through experimental evidences [25–27]. However, the sample size is small and the evidence is insufficient for a single experimental paper. In the present work, we use several bioinformatics analysis tools, and the combination of bioinformatics analysis tools could provide more sufficient evidence for survival marker validation.

Provided the high BIRC5 expression was involved in therapy response and worse prognosis, how to handle BIRC5 overexpressed patients remains a lot of confusion. Here, we showed that a number of commonly used drugs were able to modulate BIRC5. For example, cisplatin, epirubicin, doxorubicin, tamoxifen, and lapatinib could decrease BIRC5 level, while docetaxel could increase BIRC5 expression. Hormone receptors were negatively correlated with BIRC5 level as described in Figure 4, and endocrine drug tamoxifen could reduce BIRC5 level as shown in Figure 6. Therefore, it is interesting to see whether hormone receptor positive patients with BIRC5 overexpression would benefit from BIRC5 repression. We are currently enrolling patients (half cases with high BIRC5 expression and half with low expression) to evaluate the effect of BIRC5. Remarkably, BIRC5 has been found to confer resistance to chemotherapy and radiation. Targeting BIRC5 including antisense oligonucleotide, ribozyme, RNA interference, and cancer vaccine in experimental models improved survival [11,12]. Of BIRC5-related signaling pathways, ‘hippo signaling pathway’ and platinum drug resistance have been previously confirmed to be responsible for drug resistance [28]. Further investigations are needed to more precisely elucidate the relevance of these signaling pathways.

As a key component of the spindle assembly checkpoint, CDC20 has been reported in various malignant tumors and exhibits an important role in carcinogenesis and progression [24,29]. High level of CDC20 was found to be related to aggressive course of breast cancer and poor patient outcome, after 20 years follow-up of 445 patients [30]. After co-expression and correlation analysis using the Oncomine, bc-GenExMiner, and UCSC Xena web-based tools in the present study, we confirmed that CDC20 gene was positively correlated with BIRC5 expression. As a matter of fact, both CDC20 and BIRC5 were found to be co-expressed in lung adenocarcinoma, endometrial cancer, renal cell carcinoma, and thyroid carcinoma [31–34]. Given that cell cycle process is often coordinated with apoptotic proteins to maintain tissue homeostasis, silencing the expressions of cell cycle protein as well as anti-apoptotic proteins simultaneously could potentially lead to cell cycle arrest and reduce the proliferation of breast cancer cells. Recently, the CDC20 and BIRC5 small interfering RNAs delivered by additive polyplexes displayed novel therapy efficacy in breast cancer cell [35]. This pioneering research, along with our bioinformatics analysis, would add a piece of evidence to the emerging idea that BIRC5 might contribute to breast cancer progression and drug resistance associated with CDC20 expression.

**Conclusion**

The present study validated that BIRC5 was overexpressed in breast cancer patients and was responsible for a worse survival. BIRC5 might be adopted as a promising predictive biomarker and potential therapeutic target with co-expressed CDC20 gene. Further large-scale studies are needed to more precisely confirm the prognostic significance of BIRC5 in breast cancer treatment.

**Competing Interests**

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Ethics Approval
The ethics committee of the Affiliated Changzhou No.2 People’s Hospital of Nanjing Medical University approved our research. The collection and use of samples in studies were conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Changzhou No.2 People’s Hospital. Informed written consent was received from all patients.

Data Availability
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations
BIRC5, baculoviral inhibitor of apoptosis repeat containing 5; CDC20, cell-division cycle protein 20; CI, confidence interval; ER, estrogen receptor; HER-2, human epidermal growth factor receptor-2; HR, hazard ratio; NPI, Nottingham Prognostic Index; PR, progesterone receptor; SBR, Scarff–Bloom–Richardson; TCGA, The Cancer Genome Atlas.

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