Abstract. The roles of Ephrin B (EphB) receptors in cancer are relatively unknown as these receptors are associated with complex signaling pathways. A limited number of studies have investigated the association between EphB receptors and prognosis. Using the Kaplan-Meier plotter database, the present study investigated the associations between the mRNA expression levels of five EphB receptors and the outcomes of 3,554 patients with breast cancer who had been followed-up for 20 years. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated to assess the relative risk of survival. The results demonstrated that high mRNA expression levels of EphB2 (HR, 0.74; 95% CI, 0.66-0.84; P=2.1x10^{-6}), EphB4 (HR, 0.82; 95% CI, 0.72-0.93; P=0.0023) and EphB6 (HR, 0.69; 95% CI, 0.61-0.78; P=3x10^{-9}) were significantly associated with improved survival, while a high mRNA expression level of EphB3 (HR, 1.14; 95% CI, 1.01-1.28; P=0.029) was associated with worse survival for patients with breast cancer. High expression levels of all EphB receptors, including EphB1 (HR, 1.4; 95% CI, 1.02-1.94; P=0.039), EphB2 (HR, 1.34; 95% CI, 1.07-1.67; P=0.011), EphB3 (HR, 1.39; 95% CI, 1.11-1.73, P=0.0038), EphB4 (HR, 1.33; 95% CI, 1.06-1.67; P=0.013) and EphB6 (HR, 1.32; 95% CI, 1.05-1.65; P=0.016), were associated with an increased risk of mortality in patients with lymph-node-positive breast cancer. High mRNA expression levels of EphB1 were not associated with survival for all patients with breast cancer (HR, 0.85; 95% CI, 0.72-1.01; P=0.058). The results of the present suggested that EphB receptors may be useful as prognostic biomarkers of breast cancer.

Introduction

According to the American Cancer Society (ACS), breast cancer (BC) is the most common malignancy and the second most common cause of cancer-associated mortality, in the USA (1). The ACS have estimated a total of 268,670 newly diagnosed cases of invasive BC and 41,400 BC-associated mortalities among females in the USA in 2018 (1). Current treatments, including surgery, endocrine therapy, chemotherapy and radiation, have greatly improved the survival of females diagnosed with BC (2); however, a cure remains to be identified. Understanding the underlying mechanisms that contribute to the progression of this disease is important for developing novel targets.

The Ephrin (Eph) family is the largest family of tyrosine kinase receptors (TKRs). Eph proteins are subdivided into two categories, A and B, according to their sequence homology and affinity for corresponding transmembrane ephrin ligands (3,4). EphB TKRs are considered as candidates for novel anticancer therapies due to their participation in both physiological and pathological processes (5-7). It has been reported that metastatic BC cell motility may be dynamically guided by the crosstalk between epidermal growth factor-mediated chemotaxis and contact inhibition of locomotion, mediated in part by EphB receptors (8). This suggests that EphB receptors may serve a role in the recurrence of human BC (8). Other preclinical and laboratory studies have also revealed the function of EphB TKRs in tumor growth, invasion, metastasis and angiogenesis (9), including in BC (10). In the human genome there are five distinct EphB receptors, which aberrantly bind three
membrane-anchored ephrin-B ligands (11-13). This aberrant interaction between ligands and receptors results in pleiotropic functions and bidirectional signaling, which makes the role of EphB receptors in cancer complex (9). Additionally, the activities of EphB receptors in cancer remain controversial, with evidence supporting both tumor-promoting and tumor-inhibiting functions (9). Nevertheless, EphB receptors are promising candidates for novel therapeutic targets in cancer.

The present study aimed to resolve this controversy by comprehensively investigating the prognostic roles of EphB receptors in BC, including EphB1, EphB2, EphB3, EphB4 and EphB6, using a large population-based database. The Kaplan-Meier plotter (KM plotter) database (14-18) was used to calculate the relapse-free survival (RFS) from a total of 3,554 patients with BC and the mRNA-level data of EphB receptors were downloaded. Relapse-free survival was defined as the time from diagnosis to the first relapse or death as a result of any cause. The analyses performed revealed significant associations between EphB receptors and human BC progression, which, to the best of our knowledge, have not been previously investigated in BC.

Materials and methods

An online database was used to determine the association between EphB mRNA expression and RFS. At present, the database contains data regarding lung (14), ovarian (19), gastric and breast malignancies (18). The database was first set up from the Gene Expression Omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo/). The gene expression data and survival information of 3,554 patients with BC, with 20 years of follow-up, were obtained for the current study, the dataset of which was originally from Affymetrix HG-U133A (GPL96) and HG-U133 Plus 2.0 (GPL570) microarrays that have 22,277 probe sets in common (18). Briefly, survival information and mRNA levels of five individual EphB receptors, including EphB1, EphB2, EphB3, EphB4 and EphB6, were downloaded from the KM plotter database (http://kmplot.com/analysis/index.php?p=service&cancer=breast, 2018 edition) to provide KM plots. All patients with RFS available were included. The KM plotter database (http://kmplot.com/analysis/index.php?p=service&cancer=breast, 2018 edition) to provide KM plots. All patients with RFS available were included. The Kaplan-Meier plotter (KM plotter) database (http://kmplot.com/analysis/index.php?p=service&cancer=breast, 2018 edition) to provide KM plots. All patients with RFS available were included. The results of the KM plotter database were consistent and reliable, with high expression of EphB4 mRNA was positively associated with RFS in 3,554 patients with BC (Affymetrix ID: 204600_at EPHB3) is presented in Fig. 1C. In contrast to EphB2, high mRNA expression of EphB3 was associated with worse RFS. The prognostic effect of EphB4 mRNA expression was then analyzed. High expression of EphB4 mRNA was positively associated with RFS in 3,554 patients with BC (Affymetrix ID: 202894_at EPHB4; Fig. 1D). Finally, the impact of EphB6 mRNA expression on the prognosis of 3,554 patients with BC was investigated. High EphB6 mRNA expression was positively associated with RFS (Affymetrix ID: 204718_at EPHB6; Fig. 1E).

Association between EphB receptors with the clinicopathological features of patients with BC. The present study further determined the association between EphB receptors with clinicopathological features, including ER status (Table I), PgR status (Table II), HER2 status (Table III), lymph node status (Table IV) and pathological grade (Table V) of patients with BC. It should be noted that information on ER, PgR, HER2, lymph node status and pathological grade was not available for all 3,554 patients.

EphB1 expression data and ER status were available for a total of 1,008 patients, and both ER status and EphB2, B3, B4 or B6 expression data were available for 2,473 patients. For ER-positive patients, it was demonstrated that EphB1 was positively associated with RFS (HR, 0.67; CI, 0.45-0.99; P=0.044); however, EphB3 was negatively associated with RFS (HR, 1.31; CI, 1.09-1.56; P=0.0029). By contrast, in ER-negative subgroups, EphB1 (HR, 0.56; CI, 0.36-0.86; P=0.0081), EphB3 (HR, 0.76; CI, 0.59-0.98; P=0.035) and EphB6 (HR, 0.72; CI, 0.55-0.93; P=0.012) were identified to be associated with improved RFS.

As demonstrated in Table II, both EphB1 expression and PgR status data were available for 861 patients, and PgR status and EphB2, EphB3, EphB4 or EphB6 expression data were available for 1,008 patients. Only EphB1 was associated with improved RFS in PgR-negative patients (HR, 0.6; CI, 0.4-0.91; P=0.014). However, EphB2 (HR, 1.66; CI, 1.22-2.26; P=0.0012) and EphB4 (HR, 1.51; CI, 1.1-2.08; P=0.0098) expression were revealed to be associated with worse RFS in PgR-negative subgroups.

As presented in Table III, both EphB1 expression and HER2 status data were available for 785 patients, and HER2 status and EphB2, EphB3, EphB4 or EphB6 expression data were available for 924 patients. In HER2-positive patients, EphB2 (HR,
2.03; CI, 1.09-3.77; P=0.023), EphB4 (HR, 1.95; CI, 1.12-3.42; P=0.017) and EphB6 (HR, 1.77; CI, 1.05-2.94; P=0.028) were negatively associated with RFS. In HER2-negative patients with BC, EphB2 (HR, 1.52; CI, 1.15-2.02; P=0.0033) and EphB3 (HR, 1.4; CI, 1.05-1.86; P=0.019) were identified to be associated with worse RFS.

As demonstrated in Table IV, both EphB1 expression and lymph node status data were available for 1,116 patients, and lymph node status and EphB2, EphB3, EphB4 or EphB6 expression data were available for 2,758 patients. EphB1, EphB2, EphB3, EphB4 and EphB6 were all negatively associated with RFS in lymph-node-positive patients with BC. EphB3 (HR, 1.36; CI, 1.13-1.65; P=0.0014) and EphB4 (HR, 1.21; CI, 1.01-1.43; P=0.034) were revealed to be associated with worse RFS in lymph-node negative patients.

As presented in Table V, both EphB1 expression and pathological grade data were available for 675 patients, and pathological grade and EphB2, EphB3, EphB4 or EphB6 expression data were
available for 1,755 patients. EphB1 was demonstrated to be positively associated with RFS in patients with grade I BC (HR, 0.31; CI, 0.09-1.05; P=0.046). EphB2 was identified to be negatively associated with RFS in patients with grade III BC (HR, 1.29; CI, 1.05-1.58; P=0.010).
EphB3 was revealed to be associated with worse RFS in patients with grade II BC (HR, 1.39; CI, 1.06-1.82; P=0.015). EphB4 was identified to be associated with worse RFS in patients with both grade I BC (HR, 1.99; CI, 0.99-3.99; P=0.048) and grade III BC (HR, 1.31; CI, 1.02-1.68; P=0.034). EphB6 was revealed to be negatively associated with RFS in patients with grade II BC (HR, 0.77; CI, 0.59-0.99; P=0.044).

**Table V. Association of EphB receptors with pathological grades of patients with breast cancer.**

| EphB receptors | Grade | Cases (n) | HR (95% CI) | P-value |
|----------------|-------|-----------|-------------|---------|
| B1             | I     | 97        | 0.31 (0.09-1.05) | 0.046a  |
|                | II    | 187       | 1.40 (0.78-2.49) | 0.250   |
|                | III   | 391       | 0.73 (0.48-1.11) | 0.140   |
| B2             | I     | 308       | 1.70 (0.98-2.95) | 0.057   |
|                | II    | 724       | 1.29 (0.95-1.76) | 0.110   |
|                | III   | 723       | 1.29 (1.00-1.65) | 0.046a  |
| B3             | I     | 308       | 0.72 (0.42-1.24) | 0.230   |
|                | II    | 724       | 1.39 (1.06-1.82) | 0.015a  |
|                | III   | 723       | 1.22 (0.94-1.57) | 0.130   |
| B4             | I     | 308       | 1.99 (0.99-3.99) | 0.048a  |
|                | II    | 724       | 1.16 (0.9-1.51)  | 0.260   |
|                | III   | 723       | 1.31 (1.02-1.68) | 0.034a  |
| B6             | I     | 308       | 0.69 (0.4-1.18)  | 0.170   |
|                | II    | 724       | 0.77 (0.59-0.99) | 0.044a  |
|                | III   | 723       | 0.85 (0.65-1.11) | 0.240   |

P<0.05. EphB, ephrin B; HR, hazard ratio; CI, confidence interval.

**Table VI. Associations of EphB receptors with molecular subtypes of patients with breast cancer.**

| EphB receptor | Molecular subtype | Cases (n) | HR (95% CI) | P-value |
|---------------|-------------------|-----------|-------------|---------|
| B1            | Basal             | 339       | 0.75 (0.52-1.08) | 0.120   |
|               | Luminal A         | 783       | 0.81 (0.62-1.05) | 0.110   |
|               | Luminal B         | 389       | 0.57 (0.38-0.86) | 0.007a  |
|               | HER2+             | 149       | 0.58 (0.35-0.95) | 0.029a  |
| B2            | Basal             | 580       | 0.69 (0.53-0.89) | 0.005a  |
|               | Luminal A         | 1,764     | 0.70 (0.59-0.84) | <0.001a |
|               | Luminal B         | 1,002     | 0.71 (0.56-0.89) | 0.003a  |
|               | HER2+             | 208       | 0.5 (0.33-0.78)  | 0.002a  |
| B3            | Basal             | 580       | 0.74 (0.57-0.97) | 0.025a  |
|               | Luminal A         | 1,764     | 0.89 (0.73-1.08) | 0.230   |
|               | Luminal B         | 1,002     | 1.13 (0.92-1.39) | 0.240   |
|               | HER2+             | 208       | 2.00 (1.21-3.28) | 0.0066  |
| B4            | Basal             | 580       | 0.86 (0.66-1.12) | 0.260   |
|               | Luminal A         | 1,764     | 0.64 (0.53-0.77) | <0.001a |
|               | Luminal B         | 1,002     | 0.85 (0.69-1.03) | 0.100   |
|               | HER2+             | 208       | 1.36 (0.85-2.18) | 0.190   |
| B6            | Basal             | 580       | 0.70 (0.52-0.93) | 0.015a  |
|               | Luminal A         | 1,764     | 0.61 (0.51-0.72) | <0.001a |
|               | Luminal B         | 1,002     | 0.62 (0.48-0.80) | <0.001a |
|               | HER2+             | 208       | 0.50 (0.30-0.84) | 0.008a  |

P<0.05. EphB, ephrin B; HER2, human epidermal receptor 2; HR, hazard ratio; CI, confidence interval.

CI, 1.16-5; P=0.046). EphB3 was revealed to be associated with worse RFS in patients with grade II BC (HR, 1.39; CI, 1.06-1.82; P=0.015). EphB4 was identified to be associated with worse RFS in patients with both grade I BC (HR, 1.99; CI, 0.99-3.99; P=0.048) and grade III BC (HR, 1.31; CI, 1.02-1.68; P=0.034). EphB6 was revealed to be negatively associated with RFS in patients with grade II BC (HR, 0.77; CI, 0.59-0.99; P=0.044).
including basal-like, luminal-A, luminal-B and HER2-positive. As presented in Table VI, EphB1 was revealed to be associated with improved RFS in patients with luminal-B (HR, 0.57; CI, 0.38-0.86; P=0.0072) and HER2-positive BC (HR, 0.58; CI, 0.35-0.95; P=0.029). EphB2 and EphB6 were identified to be positively associated with RFS in each molecular subgroup. EphB3 was revealed to be associated with improved RFS in patients with basal-like BC (HR, 0.74; CI, 0.57-0.97; P=0.025); however, it was associated with worse RFS in patients with HER2-positive BC (HR, 2.0; CI, 1.21-3.28; P=0.0055). EphB4 was identified to be positively associated with RFS in patients with luminal-A BC (HR, 0.64; CI, 0.53-0.77; P=1.9x10^-4).

**Discussion**

The KM plotter database was generated from the GEO database. The expression data of 22,277 genes were initially available for 1,809 patients with BC (18). Gene expression data and survival information have since been validated and updated for 3,554 patients with BC. Therefore, the KM plotter can be used to analyze the prognostic effect of individual genes with clinical outcomes, including overall survival (OS) and RFS (http://kmplot.com/analysis/index.php?p=service&cancer=breast). As certain patients lacked OS data, the current study focused on RFS. The present study comprehensively and specifically analyzed the associations between the expression levels of EphB receptors, including EphB1, EphB2, EphB3, EphB4 and EphB6, and RFS in all patients with BC, as well as in subgroups according to clinicopathological features, which, to the best of our knowledge, has not previously been reported. EphA receptors were not discussed in the present study and may be investigated in future studies. EphB receptors predominantly function independently on class B ephrin ligands in BC, therefore, the current study only analyzed and discussed EphB receptors (6,9).

A limited number of studies have investigated EphB1 in patients with BC. A BC-risk, genome-wide association study suggested an association between carcinogenesis and germline-somatic rs3732568 in EphB1 (20). The current study revealed that EphB1 was not associated with RFS. In subgroup analysis, EphB1 was positively associated with RFS in patients with PgR-negative and grade I BC. Previous studies have demonstrated that EphB3 receptor can inhibit cell adhesion and migration (27). EphB4 has more widely been investigated in previous studies. It has been demonstrated that EphB2 can regulate migration in BC (27). Furthermore, the interaction of EphB6 with a number of proteins can lead to proteomic profile changes in EphB6-overexpressed MDA-MB-231 cells (44). Significantly

**EphB4 is involved in regulating mammary gland development.** EphB4 protein overexpression has been revealed to induce delayed development of the mammary gland during puberty and pregnancy (32,33). In addition, EphB4 knockdown has been demonstrated to inhibit the survival, migration and invasion of BC cells (34). Furthermore, EphB4 has been identified to promote erythropoietin-induced tumor growth in human BC (35). In one small-sample study, patients with HER2-positive BC with EphB4 and EphB2 overexpression were associated with a shorter survival time (36). However, to the best of our knowledge, high expression of EphB4 alone remains to be identified as an independent prognostic factor. On the contrary, another study revealed negative associations between EphB4 and clinical outcomes by investigating protein expression in breast tissue microarrays (37). Notably, dual functions of this receptor in tumor promotion and inhibition have been reported on the basis of its ligand presence or absence (9,38). Previous studies have been based on small samples. In the present large analysis it was identified that EphB4 mRNA levels could predict improved RFS in all patients with BC, while it was associated with worse RFS in PgR-negative, HER2-positive, grade I and grade III subgroups, which supports the dual function of EphB4 (10,34,39). EphB4 activation leads to cell proliferation and enhanced migration via the phosphoinositide 3-kinase (PI3K)/Akt pathway (40). However, in a mouse xenograft model, EphB4 was demonstrated to inhibit cell growth via the Abl-Crk pathway (10).

EphB6 is an uncommon Eph receptor and lacks catalytic capacity due to its kinase domain changes (41). In an experiment conducted in vitro, reduced EphB6 receptor expression resulted in increased metastatic activity in BC (41). Other studies have demonstrated that EphB6 transcriptional silencing and its consequent effects on the Wnt pathway may contribute to tumor progression in triple-negative BC (42). Additionally, EphB6 receptors with kinase deficiency have been demonstrated to initiate signal transduction from the cell surface to the nucleus, allowing for the expression of a variety of genes alterations that are involved in tumor progression via the PI3K/Akt/mammalian target of rapamycin pathways (43). Furthermore, the interaction of EphB6 with a number of proteins can lead to proteomic profile changes in EphB6-overexpressed MDA-MB-231 cells (44). Significantly
positive associations have been revealed between EphB6 and OS in BC tissue microarrays (37). In the present study, high expression of EphB6 mRNA predicted a longer RFS in all patients with BC. In the subgroup analysis, EphB6 was associated with improved RFS in patients with ER-negative and grade II BC, but was associated with worse RFS in patients with HER2-positive BC, which indicates a dual function of EphB6.

Expression of EphB2 mRNA has been demonstrated to predict poor survival in lymph-node-positive BC (45). Notably, all EphB receptors were associated with worse RFS in patients with lymph-node-positive BC in the present study.

In addition, we attempted to investigate the prognostic value of the expression of EphB receptors in another independent METABRIC dataset through the cBioPortal for Cancer Genomics (cbioportal.org) (46,47). The genomic profiles of 2,509 patients with BC were available in the dataset, with data of somatic mutations, copy number alterations and gene expression. However, the detailed clinicopathological features or the best performing thresholds could not be determined using METABRIC. Therefore, important results could have been missed using the cBioPortal; the data have not been presented in the current study.

The functions of ephrin receptors in cancer are paradoxical and complex (48). The ephrin system is essentially present in all types of cancer cell (48). Cancer cellular phenotypes may partly be attributed to a combinatorial expression or interactions of ephrin receptors among the same class, as well as two different classes. For example, EphB6, a receptor with kinase-deficiency, can interact with EphB2 or EphA2 in mammalian cells (49). EphB4 can promote cancer progression independent of EphB6, suggesting that the balance may determine tumorigenesis in the EphB4-EphB6 system (41). Decreased ephrin expression levels have also been associated with tumor progression (50). Consistent with the dichotomy, evidence has demonstrated that ephrin receptors and ephrins exhibit both tumor-promoting and -suppressing activities. For example, in the present study high mRNA expression of EphB3 predicted shorter RFS in ER positive patients but longer RFS in ER-negative patients. Additionally, EphB6 indicated longer RFS in patients with ER-negative BC but a shorter RFS in patients with HER2-positive BC, which suggests the multifaceted roles of these receptors. The underlying mechanisms responsible for these divergent functions have previously been investigated (7,50,51).

The results of the current study are limited for two reasons. First, the database lacks information on clinicopathological features in certain patients, which may lead to statistical bias. Second, multivariate analysis cannot be used in the database to correct the associations between different clinicopathological features. Nevertheless, the comprehensive data suggest that EphB receptors are prognostic factors and traceable targets for BC, which may improve understanding regarding the complexity and heterogeneity of BC molecular biology. In addition, the current results may assist the development of tools to more accurately predict prognosis and design customized therapies. ELISA can be used as a rapid and sensitive method to detect EphB4 as diagnostic and therapeutic biomarker in BC (45). EphB6 deficiency may be treated by small molecule inhibitors in a synthetic lethality approach (52). Biological products targeting EphB receptors, including antibodies, peptides and recombinant proteins, to reduce the progression of several types of cancer, such as BC, are in the preclinical stages of investigation in animal models. Additionally, at present, certain biopharmaceutical agents are undergoing phase I or phase II clinical trials (e.g., NCT01642342, NCT03552796, NCT02495896) (53-55).

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Availability of data and materials

The datasets used during the current study are available from Kaplan-Meier Plotter (http://kmplot.com).

Authors' contributions

XM, OH and XZ conceived and designed the study. XZ and OH performed the statistical analysis. MJ, ZL and DC analyzed the data. XZ and XM wrote the manuscript.

Ethics approval and consent to participate

Not applicable.
Patient consent for publication
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Competing interests
The authors declare that they have no competing interests.

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