Original Article

Predictive potential of hepatocyte growth factor and bone morphogenetic proteins in lymphatic metastasis of breast cancer

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Background: Lymph node metastasis is an important predictive factor for the prognosis of breast cancer. Bone morphogenetic protein (BMP) and hepatocyte growth factor (HGF), and its receptor MET, are involved in metastasis. However, their predictive potential in the prediction of lymph node metastasis from breast cancer has not been evaluated to date. The aim of this study is to evaluate the implication of HGF and BMPs in breast cancer lymphatic metastasis.

Methods: The association between the ligands and receptors of BMP, the regulators of HGF, and the modulators of MET were detected in Cardiff clinical breast cancer cohort and The Cancer Genome Atlas (TCGA) breast cancer ribonucleic acid (RNA) sequencing database. Predictive model of HGF and BMPs for nodal metastasis was evaluated by binary logistic regression and receiver operating characteristic (ROC) curve.

Results: BMP-2 expression was upregulated but BMP-7 and matriptase-2 expression were downregulated in patients with nodal metastases. MET, matriptase-1, BMP-15, HAI-1, and matriptase-2 were correlated with the lymphangiogenesis markers. Lymphatic metastasis was positively with MET, matriptase-1 and BMP-15 but was negatively with matriptase-2, BMP-3, and HAI-1. ROC curve analysis showed the six factors with nodal status had a significant area under the curve values (0.657, P=0.001). The integrated signature could effectively predict lymph nodes involvement (P=0.006, hazard ratio =2.929).

Conclusions: The aberrant expression of HGF/MET and BMPs is related to lymphatic metastasis in breast cancer. Integrated expression level of MET/BMP-15/matriptase-1 and the inversed HAI-1/BMP-3/matriptase-2 establishes a predictive model for lymph node involvement.

Keywords: Breast cancer; lymphatic metastasis; hepatocyte growth factor (HGF); bone morphogenetic proteins (BMPs)

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Introduction

Background

Breast cancer is the most prevalent malignancy worldwide with a high mortality rate. Lymphatic metastasis is a common disseminating route in breast cancer patients. The incidence of lymphatic metastasis varies between 23.8% to 35.4% in early breast cancers (1-3). The main reason for the failure of regional therapy is the recurrence of lymph node metastases which can progress to advanced breast cancer with distant metastasis. The metastatic status of the locoregional lymph nodes is an independent prognostic indicator, as patient survival decreases with an increased number of lymph nodes involved (4). Therefore, lymph

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node metastasis presents an important factor when selecting regional and systemic therapies (5). The factors associated with lymph node metastasis including tumour size, gender, lymphatic vessel invasion and other clinical characteristics. Larger tumours are more prone to lymph node metastasis than tumours of smaller size (5). Draining lymphatic vessels in male breasts are shorter than in female which confers a short route for axillary lymph node metastasis although male cases are rare (6). With advances in breast surgery and radiotherapy, the management of lymph node metastasis has been improved which de-escalated from a radical removal of lymph nodes to sentinel lymph node biopsy (SLNB), even an omission of invasive operations for axillary lymph nodes (7). Much remains unknown about the molecular and cellular mechanisms of lymphatic metastasis although it has been explored for decades.

Rationale and knowledge gap

Hepatocyte growth factor (HGF) can elicit multiple functions which requires activation by HGF activator (HGFA) and matriptases, is negatively regulated by HGFA inhibitor (HAI) (8). HGF promotes both invasion and metastasis in breast cancer (9,10). Increased HGF levels in primary tumours were shown as an independent indicator for worse prognosis in patient with breast cancer (11). Kim *et al.* [2016] found that the regional lymph node metastasis rate was higher in HGF-high-expressing tumour than in low expressing tumour (98.3% *vs.* 85.2%, P=0.017). Although higher HGF expression correlated with a better relapse-free survival (106 *vs.* 85 months, P=0.008), its relationship with treatment response suggests that additional factors may influence long-term outcomes (12).

MET is the pathway receptor of HGF which is a known oncogene. The HGF/MET signalling is initiated when HGF binds with the MET extracellular domain with a subsequent dimerization of the receptors, leading to a phosphorylation of specific tyrosine (Y1234 and Y1235) residues at its intracellular kinase domain (13). This hyperactivation allows cancer cells to acquire migratory and invasive abilities, thus enabling cancer cells to spread from the primary tumour to distant sites (14,15). However, the regulatory mechanisms of lymph node metastasis might also be affected by other factors in the HGF/MET pathway, for instance, HGFA, HAI-1 and HAI-2, etc., which remain largely unknown for their roles in the lymphatic involvement.

Through the analysis of The Cancer Genome Atlas (TCGA) breast cancer ribonucleic acid (RNA) sequencing database, it is found that HGF/MET has a significant correlation with bone morphogenetic proteins (BMPs), such as BMP-2 and BMP-4 (16). BMPs are the members of transforming growth factor beta (TGF-β) superfamily and are important regulators of cell proliferation, differentiation and motility being vital for foetal development, tissue regeneration and homeostasis (17). BMPs are multifunctional proteins regulating cell growth, differentiation, migration, invasion, apoptosis and epithelial-mesenchymal transition in breast cancer cells (18). In the dissemination to bone of breast cancer cells, BMP-7 plays a negative role by inhibiting the formation of skeletal metastasis (19). BMP-2 exhibits a different role in the development of breast cancer, which enhances the abilities of invasion and migration in cancer cells and promotes tumour-associated angiogenesis (20-22). Similarly, BMP-4 enhances the abilities of invasion and migration but suppresses the ability of migration in breast cancer cells (23,24). BMP-6 inhibits proliferation and apoptosis but promotes differentiation and migration of breast cancer cells (20). Interactions between tumour cells and microenvironment can be regulated by BMPs through influencing other growth factors and pathways (25).

There are two pathways for signal transduction of BMPs which are Smad-dependent pathway and Smad-independent pathway (26). The receptors of BMP include type-I and type-II BMP receptors (26). The cell growth inhibition by BMPs is often executed by BMP/BMP receptors/Smad-induced cell-cycle inhibitors, cyclin-dependent kinase

Highlight box

Key findings

- The aberrant expression levels of hepatocyte growth factor/MET and bone morphogenetic proteins (BMPs) could influence the status of lymph node metastasis in breast cancer.

What is known and what is new?

- The MET/matriptase-1/BMP-15 and the inversed matriptase-2/BMP-3/HAI-1 are significantly connected with lymph node metastasis.
- Matriptase-1, BMP-15 and reverse HAI-1, reverse matriptase-2, and reverse BMP-3 establish a predictive model for lymph node involvement and could identify nodal metastasis.

What is the implication, and what should change now?

- The proposed prediction model may help to guide the regional management and system treatment of clinical practice in breast cancer.

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inhibitor (CDKN) 2B, CDKN1A and CDKN1C (27). BMPs are the important proliferation regulator to breast cancer cells and each BMP makes a different effect on the growth of cells. BMP-2, BMP-6 and BMP-7 inhibit the proliferation function but BMP-4 stimulates the growth of breast cancer cells (17). In addition to the synergistic effect between BMP and HGF, HGF-induced expression of certain BMPs, BMP receptors and co-receptors has been evident in prostate cancer cells and vascular endothelial cells (28-30).

Objective

Both BMPs and HGFs are actively involved in the angiogenesis and the lymph node metastasis of breast cancer (31,32). However, their potential in the prediction of lymph node metastasis from breast cancer has not been fully explored. The present study is aimed to conduct a comprehensive evaluation of both HGF and BMPs for their implication in lymph node metastasis of breast cancer. We present this article in accordance with the TRIPOD reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-25-18/rc).

Methods

Clinical materials collection

The excised breast cancer tissues (n=127) and normal breast tissue (n=34) were collected and processed immediately during the operation (31). The results of postoperative histopathology and molecular pathology were collected and verified by a consultant pathologist. The median follow-up time for patients after surgery was 120 months.

RNA extraction, reverse transcription, and quantitative polymerase chain reaction (qPCR)

Total cellular RNA was isolated from the collected breast cancer tissues, normal breast tissue. After identifying the concentration and quality of RNA by spectrophotometric measurement (WPA UV 1101; Biotech Photometer, Cambridge, UK), complementary DNA (cDNA) was obtained by reverse transcription (Sigma, Poole, Dorset, UK). The method of qPCR has been published in our previous study (33). BMP-9 primers were as follows: 5'-ACTGAA CCTGACCGTACACAGTCACGAGGAGGACAC-3' (forward) and 5'-GATGTCCTCGAAGTTTACCC-3' (reverse). The primers for HGF, MET, matriptase-1, matriptase-2, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), phage display peptide library (PDPL), vascular endothelial growth factor (VEGF) A, VEGFC, VEGFD, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-10, BMP-11, BMP-12 and BMP-15 were previously reported (8-10,15,29,30,33,34) and the quantitative data were employed for statistical analyses to further dissect their implication in lymph node metastasis in the present study.

TCGA breast cancer RNA sequencing data

The relation between the aberrant expression of HGF/MET/BMPs and the lymph node metastasis in breast cancer was analysed using TCGA (https://portal.gdc.cancer.gov) database. The RNA sequencing dataset comprises 493 cases with no lymph node involvement and 587 cases with lymph node involvement in the cohort of primary breast cancers.

Statistical analysis

The comparison of genes expression levels in lymph node metastasis was used by Mann-Whitney test. The correlation between these genes and lymphatic metastasis in breast cancer was performed by binary logistic regression. The predictive model of lymphatic involvement was established by receiver operating characteristic (ROC) curve. All data analysis was performed by SPSS (Version 27, IBM UK Ltd., Portsmouth, UK).

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Bro Taf Health Authority Local Research Ethics Committee (No. 01/4303) and informed consent was obtained from all individual participants.

Results

Aberrant expression of HGF/MET in breast cancer developed lymph node metastases

Compared with primary tumours without lymph node metastasis, matriptase-2 was significantly reduced in those tumours with lymphatic metastases (P=0.03) though the

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Table 1 Aberrant expression of HGF/MET and lymph node metastasis in breast cancer from Cardiff University database

Variable	LN (–) (n=72)	LN (+) (n=55)	P value
HGF	8 (0–26.5)	3 (0–39.5)	0.97
MET	5,140 (1,250–14,400)	4,710 (1,147–27,300)	0.77
HAI-1	394 (52–816)	216 (47–1,276)	0.89
HAI-2	209.5 (31.5–591.3)	265 (30.0–692.5)	0.66
HGFA	11.85 (1.05–36.18)	13.5 (1.8–49.2)	0.43
Matriptase-1	0 (0–0)	0 (0–0.1)	0.43
Matriptase-2	0 (0–0.1)	0 (0–0.005)	0.03

Data are presented as median (interquartile range). HGF, hepatocyte growth factor; LN, lymph node.

Table 2 HGF/MET and LN metastasis in breast cancer (TCGA BRCA)

Variable	LN (–) (n=493)	LN (+) (n=587)	P value
HGF	32.92 (16.27–67.61)	44.67 (22.72–77.61)	0.81
MET	357.68 (135.81–774.36)	325.10 (148.29–691.10)	0.08
HAI-1	3,838.54 (2,955.02–5,147.01)	4,121.36 (3,145.39–5,594.98)	0.07
HAI-2	10,650.60 (8,156.67–14,754.55)	10,330.43 (7,684.82–13,731.24)	0.18
HGFA	0.90 (0.00–2.80)	0.75 (0.00–2.54)	0.17
Matriptase-1	3,106.91 (2,074.60–4,448.86)	2,724.01 (1,948.03–4,301.17)	0.006
Matriptase-2	37.60 (5.02–182.81)	50.19 (6.33–172.89)	0.99

Data are presented as median (interquartile range). HGF, hepatocyte growth factor; LN, lymph node; TCGA, The Cancer Genome Atlas.

overall expression level was low. A declining trend was seen in the expression of HGF, MET, HAI-1 and matriptase-2 while elevated levels of HAI-2, HGFA and matriptase-1 appeared in the primary tumours, which presented lymph node metastases but none of these changes was statistically significant (details in *Table 1*).

According to the TCGA breast cancer database, the expression of HGF, HAI-1 and matriptase-2 tended to be increased whilst MET, HAI-2 and HGFA appeared to be decreased, in comparison with the lymph node negative group, though none of these were statistically significant. Moreover, matriptase-1 was significantly increased in the primary tumours that presented positive lymph nodes (P=0.006). The results are shown in *Table 2*.

Deregulated BMPs and their implication in lymphatic metastasis

In addition to the previously reported roles of BMPs in breast cancer, in the current study, we also evaluated the expression of BMP-9 and BMP-11 for their possible role in the lymph node metastasis. By comparing with the expression in primary tumours without lymph node metastasis, neither BMP-9 nor BMP-11 exhibited a significant change, though the expression of both genes appeared to be marginally lower in those tumours that had regional lymph node metastases, in the Cardiff breast cancer cohort (*Table 3*).

In the TCGA breast cancer database, a trend of reduction was noticed for BMP-8B in tumours which presented lymph node metastases, whilst no difference was seen for both BMP-9 and BMP-11, but none of these were statistically significant (*Table 4*).

HGF/MET, BMPs and lymphangiogenesis markers in breast cancer

Possible involvement of HGF/MET and BMP in lymph node metastasis was further evaluated by analysing their correlation with lymphangiogenic markers, in the

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Table 3 Comparison of BMPs expression between LN negative and positive from Cardiff University database

Variable	LN (–) (n=72)	LN (+) (n=55)	P value
BMP-8	0.57 (0.03–6.06)	0.44 (0.04–6.55)	0.89
BMP-9	0.0057 (0.0003–0.0606)	0.0044 (0.0004–0.0655)	0.89
BMP-11	0 (0–1)	0 (0–3.1)	0.95

Data are presented as median (interquartile range). BMP, bone morphogenetic protein; LN, lymph node.

Table 4 Comparison of BMPs expression between LN negative and positive from TCGA database

Variable	LN (–) (n=493)	LN (+) (n=587)	P value
BMP-8B	70.64 (33.58–144.24)	61.92 (29.21–127.50)	0.35
BMP-9	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.21
BMP-11	124.87 (85.87–181.00)	126.20 (90.34–172.84)	0.43

Data are presented as median (interquartile range). BMP, bone morphogenetic protein; LN, lymph node; TCGA, The Cancer Genome Atlas.

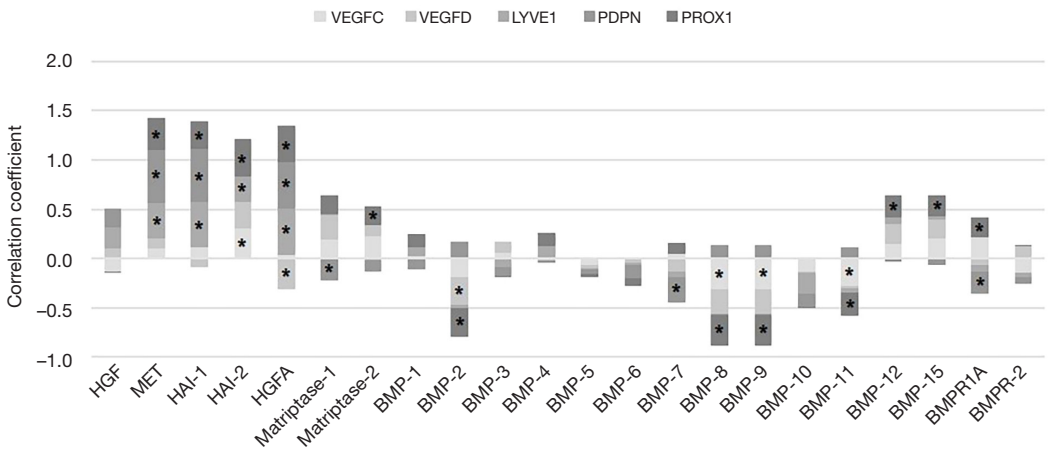

Figure 1 HGF/MET, BMPs and lymphangiogenic markers. Correlations between HGF/MET, BMPs and lymphangiogenic markers with Spearman tests are shown. *, P<0.05. BMP, bone morphogenetic protein; HGF, hepatocyte growth factor.

Cardiff cohort of breast cancer with their transcript levels previously reported (8-10,15,29,30,33,34) (*Figure 1*). MET was significantly correlated with the lymphangiogenesis markers of lymphatic vessel endothelial hyaluronan receptor-1 (LYVE1), podoplanin (PDPN) and prospero homeobox 1 (PROX1) with a correlation coefficient (r) being 0.359, 0.543, 0.324, respectively, P=0.002. HAI-1 presented a positive correlation with LYVE1, PDPN and PROX1 (r=0.459, 0.534, 0.280, respectively, P=0.06). HAI-2 presented a positive correlation with VEGFC, LYVE1 and PROX1 (r=0.309, 0.268, 0.379, respectively, P=0.01). HGFA was inversely correlated with VEGFD (r=–0.316, P=0.03) but positively correlated with LYVE1, PDPN and PROX1 (r=0.47, 0.472, 0.369, respectively, all P<0.001). Matriptase-1 was inversely correlated with PDPN significantly (r=–0.224, P=0.03), whilst matriptase-2 showed a positive correlation with PROX1 (r=0.201, P=0.043). In addition to the HGF/MET, BMPs also showed association with lymphangiogenesis markers. BMP-2 was negatively correlated with VEGFD and PROX1 (r=–0.276, –0.298, respectively, all P=0.04, 0.001). BMP-7 was negatively correlated with PDPN (r=–0.26, P=0.07. BMP-8, BMP-9 and BMP-11 were negatively correlated with VEGFC (r=–0.31, –0.31, –0.282, respectively, P=0.005, 0.005,

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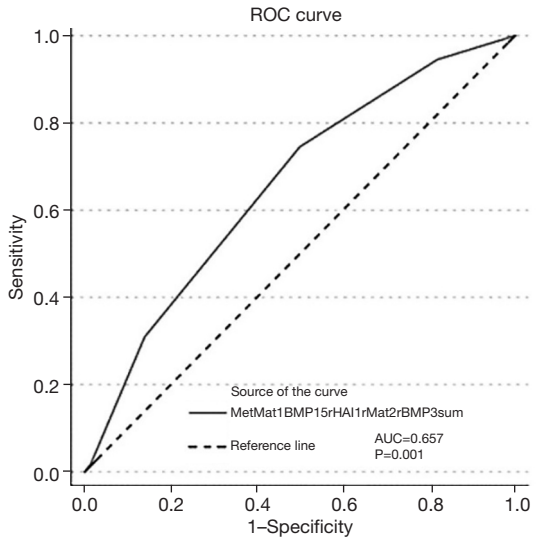

Figure 2 ROC curve of integrating these six prospective factors. AUC, area under the curve; ROC, receiver operating characteristic.

0.01) and PROX1 (r=–0.311, –0.311, –0.243, respectively, P=0.001, 0.001, 0.009). BMP-12, BMP-15 and BMPR1A presented a positive correlation with PROX1 (r=0.23, 0.214, 0.209, respectively, P=0.02, 0.03, 0.03). Furthermore, BMPR1A was negatively correlated with PDPN (r=–0.226, P=0.02). More details of HGF/MET, BMPs and lymphangiogenesis markers are shown in *Figure 1*.

Predictive potential of HGF and BMPs in lymph node metastasis

Table 1 shows matriptase-2 negatively associated with lymphatic involvement, with significance in the Cardiff cohort. Meanwhile, matriptase-1 also showed an association with lymphatic involvement in the TCGA cohort. Furthermore, HAI-1 (B=–3.07, P=0.045) and BMP-3 (B=–2.283, P=0.04) had a significantly negative correlation with lymph node metastasis, when the median expression levels were employed respectively in the logistic regression analyses, whilst MET (B=2.19, P=0.11), matriptase-1 (B=1.863, P=0.08) and BMP-15 (B=1.933, P=0.10) were more likely positively associated with lymph node metastasis.

Integrating these prospective factors of MET, matriptase-1, BMP-15 and reverse HAI-1, reverse matriptase-2 and reverse BMP-3, ROC curve analyses returned a significantly value against the involvement status of lymph node (area under the curve =0.657, P=0.001), with an optimal cut-off value at 2.5 (*Figure 2*). When a cut-off value of 3 was applied, the combined six-factor index exhibited a significant prediction value of lymph node involvement (P=0.006, hazard ratio =2.929).

Discussion

In addition to the blood circulation, another common disseminating route of breast cancer is regional lymph nodes, such as axillary lymph nodes. The metastasis status of axillary lymph nodes is a central player in identifying the clinical and pathological staging and guiding the disease management strategies of regional and systemic therapies. For example, a high axillary tumour burden in patients with lymph node metastasis requires more exhaustive radiotherapy and systemic treatment to control regional lesions. Axillary lymph node dissection has been replaced by SLNB, which is a minimally invasive staging technique. To date, non-invasive approaches are under development to identify axillary lymph node metastasis. For instance, a machine learning-based radiomics model may assist the preoperative individualized prediction of axillary lymph nodes status, by using F-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with breast cancer (35). Van Zee *et al.* established a clinical factors nomogram, for predicting the likelihood of additional lymph node metastasis in breast cancer patients with sentinel lymph node involvement (36). However, key molecules involved in the molecular and cellular machinery of lymphatic metastasis are yet to be explored for their potential in the pioneering studies of novel predictive approaches.

With the development of molecular biological techniques, different kinds of molecules were identified in the progress of lymphangiogenesis, lymphatic vessel invasion and lymph node metastasis. Generally, deregulation of the lymphatic metastatic molecules can occur earlier than the clinical detection of lymph node metastasis. The induction or activation of lymphatic vessels by lymphangiogenic cytokines from a tumour, increases the probability of tumour cells disseminating through lymphatic vessels (37). Among those regulatory factors of angiogenesis and lymphangiogenesis, aberrant levels of HGF, MET, HGFA, HAI-1 and HAI-2 have been revealed in breast cancer (8,34,38). HAI-1 and HAI-2 were expressed to an extremely lower level in poorly differentiated breast tumours, and reduced HAI-2 expression was associated with nodal involvement and poor prognosis, indicating a profound role of the HGF regulatory

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factors in the progression of breast cancer (8). Furthermore, increased levels of serum HGF have been associated with axillary lymph node metastases, histological evidence of venous invasion and relapse in breast cancer (12,39). The expression of HGF has a core role in lymphangiogenesis and lymph node metastasis in patients with breast cancer.

The activation of HGF is affected by the associated regulation factors and then influences the function of breast cancer cells. In this study, a comprehensive evaluation was conducted by focusing on HGF in conjunction with BMPs, for their implication in lymph node metastasis in breast cancer. MET, matriptase-1, BMP-2, BMP-7, BMP-8, BMP-9, BMP-11, BMP-12, BMP-15, BMPR-1A, HAI-1 and matriptase-2 were correlated with the lymphangiogenesis markers, which prompted these molecules to take part in the development of lymphatic metastasis. However, our recent study found that BMP-2, BMP-3 and BMP-6 were positively correlated with lymphangiogenesis markers in TCGA-BRCA and E-MTAB-6703 cohorts (40). Those findings appear to be different from the present study, in which BMP transcripts were normalised against cytokeratin 19 (CK19), to exclusively analyse the gene expression in epithelia and epithelia-derived cancerous cells. On the other hand, geographic factors, sample size, stage of disease and distribution of subtypes shall also be considered in relation to the different findings. Digital microdissection, in those publicly available datasets, can be employed for further analysis, with specified experimental validation in future. Furthermore, our present results showed that the aberrant expression of matriptase-1 and matriptase-2 was different between lymph node negative and positive, which means the two molecules have different roles in lymphatic metastasis. This finding is consistent with a previous study from the host laboratory, which showed that matriptase-2 inhibits both invasion and motility of breast cancer cells and has an opposing effect to matriptase-1, in the prognosis of breast cancer patients (33). Similarly, the high expression of HAI-1 inhibits the activity of HGFA and reduces the production of bioactive HGF however, the elimination expression of HAI-1 promotes migration, invasion and proliferation of breast cancer cells (34). In our analysis of the clinical cohort, HAI-1 and BMP-3 presented a negative correlation with lymph node metastasis, whilst MET, matriptase-1 and BMP-15 exhibited a positive association. An integration of these putative factors, including MET, matriptase-1, BMP-15 and inverse values of HAI-1, matriptase-2, and BMP-3, showed a significant potential of predicting lymph node metastasis. The results of our study showed, that the decreased expression of HAI-1 and matriptase-2 and the increased expression of matriptase-1 may result in strengthened activation of HGF/MET signalling. This is in line with a previous study at the host lab for HGF-promoted lymphangiogenesis markers mediated by HGF in prostate cancer (41,42). Meanwhile, the decreased expression of BMP-3 and the increase of BMP-15 may facilitate the HGF/MET-promoted invasive traits of breast cancer cells which is yet to be further investigated.

Conclusions

In conclusion, the aberrant expression levels of HGF/MET and BMPs could influence the status of lymph node metastasis in breast cancer. The MET/matriptase-1/BMP-15 and the inversed matriptase-2/BMP-3/HAI-1 are significantly connected with lymph node metastasis. Matriptase-1, BMP-15 and reverse HAI-1, reverse matriptase-2, and reverse BMP-3 establish a predictive model for lymph node involvement and could identify nodal metastasis effectively. The proposed prediction model may help to guide the regional management and system treatment of clinical practice in breast cancer.

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Footnote

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Data Sharing Statement: Available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-25-18/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Bro Taf Health Authority Local Research Ethics Committee (No. 01/4303) and informed consent was obtained from all individual participants.

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