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Expression of autocrine motility factor receptor (AMFR) in human breast and lung invasive micropapillary carcinomas

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Abstract

The aim of this study was to evaluate the clinicopathological significance of autocrine motility factor receptor (AMFR) expression in a variety of human invasive micropapillary carcinomas (IMPC). AMFR expression was compared in 111 samples of a variety of human IMPCs which had intrinsic non-micropapillary components and with 26 cases of control pulmonary adenocarcinoma (CPA, carcinoma without an IMPC component) by immunohistochemistry (IHC). In the 137 cases analysed, AMFR expression was significantly elevated in the IMPC components compared to the non-IMPC components ($p = .005$) and normal tissues ($p < .001$). AMFR expression was also higher in the IMPC samples compared to their intrinsic non-IMPC components ($p = .0234$). Between the 69 cases of lung IMPC and 26 cases of CPA, AMFR expression was notably higher in the IMPC components than in the CPA components ($p = .0455$). However, there was no significant difference between the non-IMPC components in the lung and the CPA components ($p = .4584$). Moreover, in breast cancer, elevated AMFR expression was not significantly correlated with mixed type or pure type IMPC ($p = .5969$) or with age, gender, T stage, or lymph node metastasis (LNM). Between IMPC and CPA of the lung, there was no statistical significance in age, T stage, and LNM, where AMFR expression was higher in IMPC ($p = .0071$). Thus this study demonstrated that AMFR was overexpressed in a variety of human IMPC components compared with non-micropapillary components. This suggests that AMFR expression is a potential new prognostic indicator for different types of human IMPC, which might thus be a new therapeutic target.

KEYWORDS

AMFR, Gp78, immunohistochemistry, invasive micropapillary carcinoma

1 | INTRODUCTION

Invasive micropapillary carcinoma (IMPC) was first described in breast cancer by Siriaunkgul and Tavasoli in 1993.[1] IMPC is characterized by a pseudopapillary arrangement of morule-like tumour cell clusters with reverse polarity floating in the empty stromal space, considered an "inside-out" growth pattern.[2] This aspect is confirmed by inverted immunohistochemical MUC1 expression, lack of MUC2 staining, and loss of or altered pattern of E-cadherin expression. Interestingly, tumour cells express mesenchymal markers (vimentin) and

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nuclear localization of SMAD4, which suggests epithelial-mesenchymal-transition.[3–5] Despite the low incidence of IMPC, it shows a high propensity for lymphovascular invasion (LVI) and lymph node metastasis (LNM) compared with invasive ductal carcinoma (IDC).[6,7] To date, IMPC has been reported in the breast,[1] lung,[8] urinary bladder,[9] colo-rectum,[10] stomach,[11] pancreas,[12] salivary gland,[13] thyroid,[14] uterine cervix,[15] and kidney.[16]

Using bioinformatics methods, we analysed specific IMPC gene expression signatures (GSE66418) in the Gene Expression database (http://www.ncbi.nlm.nih.gov/geo/, Gene Expression Omnibus, GEO), to determine the gene expression profile differences between IMPC and invasive ductal carcinoma of the breast. We found that autocrine motility factor receptor (AMFR) was one of the genes significantly increased in IMPC.

Since the mid-1980s, multiple groups have linked the expression of autocrine motility factor/phosphoglucose isomerase (AMF/PGI) and its receptor, AMFR, to increase metastasis and poor prognosis in cancer patients.[17] AMFR is an internalizing cell surface receptor that also exhibits ubiquitin E3 ligase activity in the endoplasmic reticulum.[17] Stimulation of AMFR by its ligand AMF/PGI alters cellular adhesion, proliferation, motility, and apoptosis.[17] In human cancers, AMFR expression correlates with aggressive cancer biology and a worse outcome for cancers of the lung, tongue, oesophagus, stomach, colon, rectum, liver, breast, thymus, skin, odontogenic tumours, and clear cell-renal cell carcinoma.[17–19] Notably, in bladder, colorectal, gastric, skin, oesophageal, and human prostate cancer, AMFR is either absent or expressed at significantly lower levels in adjacent normal tissues.[17,20]

To evaluate the clinicopathological significance of AMFR expression in human IMPC, we analysed 111 cases of IMPC, including 69 cases of lung, 33 cases of breast, 5 cases of urinary tract, and 1 case each of gastric, rectal, pancreatic and cervical IMPC. We compared the expression of AMFR in the IMPC components with the its expression in the intrinsic non-micropapillary components from the same case via immunohistochemistry (IHC).

2 | MATERIALS AND METHODS

2.1 | Patients and tissues

IMPC was defined as adenocarcinoma with a micropapillary component in which the area of the micropapillary histological subtype exceeded 5% of the tumour. One block of each tumour was examined.

We analysed 111 cases of IMPC from the Qilu Hospital of Shandong University, China between 2013 and 2015. As shown in Table 1, there were 69 cases of lung IMPC (35 females and 34 males with an average age of 55 years old) and 40 of these cases had LNM. The lung IMPC were mixed with other adenocarcinoma components. We also collected 26 cases of CPA without IMPC. This sample included 19 females and 7 males with average age of 59.7 years old, and 13 of the cases had LNM. Most of the 26 cases of CPA were mixed type adenocarcinoma, except 1 case of fetal type adenocarcinoma. The predominant components included 16 cases of acinar, 4 cases of papillary, 3 cases of lepidic, and 2 cases of solid adenocarcinoma. We analysed breast IMPC ($n = 33$, 24 cases of mixed type and 9 cases of pure type) from females with an average age of 48 years old; 23 of the cases had LNM (9 pure type cases, all had metastasis). We also collected other rare cases including urinary tract ($n = 5$, 3 cases of mixed type and 2 cases of pure type), gastric ($n = 1$), rectus ($n = 1$), pancreas ($n = 1$), and cervix ($n = 1$) cancers, and the latter 4 cases were all mixed type of IMPC. 4 of the rare cases had LNM. We compared the expression of AMFR in the IMPC components with the intrinsic non-micropapillary components, as well as with the CPA cases, via IHC. We also

TABLE 1 Clinicopathological features of the research cases

		Case Num.	Average age (year)	Gender		LN	
				Female	Male	M	Non-M
Pulmonary	IMPC	69	55	35	34	43	26
	CPA	26	59.7	19	7	13	13
Breast	IMPC (mixed type)	24	48.3	24	0	17	7
	IMPC (pure type)	9	47.3	9	0	9	0
Urothelial	IMPC (mixed type)	3	64.3	0	3	1	2
	IMPC (pure type)	2	67	0	2	1	
GI	IMPC	2	55.5	0	2	2	0
Cervix	IMPC	1	72	1	0		
Pancreas	IMPC	1	69	0	1		1

analysed the correlation between the clinicopathologic features of IMPC with AMFR expression.

This study was approved by the Ethics Committee of the Qilu Hospital of Shandong University. Informed consent to use patient tissues for the study and to reveal medical history for publication was obtained before submitting this manuscript.

2.2 | IHC

IHC was performed using an antibody against AMFR (1:800, Abcam, London, UK, ab76841) on paraffin-embedded tissue sections. Sections were subjected to antigen retrieval for 4 minutes under high pressure in citric acid buffer (pH = 6.0). The slides were evaluated by two experienced pathologists. Phosphate-buffered saline (PBS) served as a negative control. For each sample, we observed the whole slide to distinguish IMPC and other adenocarcinoma components. Staining intensity was scored as follows: 0 = negative, 1 = weak, 2 = moderate, and 3 = strong. The positive ratio per tumour area was defined as (0: 0%, 1: 1%–10%, 2: 11%–20%, 3: 21%–30%, 4: 31%–40%, 5: 41%–50%, 6: 51%–60%, 7: 61%–70%, 8: 71%–80%, 9: 81%–90%, 10: 91%–100%). The positive cell score multiplied by the intensity score was considered the final score, which ranged from 0 to 30. We used receiver operator characteristic (ROC) curves to demonstrate the cut-off point for AMFR low expression and high expression to distinguish IMPC and non-IMPC components, where specificity plus sensitivity obtained the maximum value.

2.3 | Statistical analysis

SPSS software (Version 15.0) and GraphPad Prism 6 (GraphPad Software, Inc., San Diego, CA, USA) were used for statistical analysis. Two-tailed Student's *t* test was used to evaluate the final score between different groups. Two-tailed Chi-square test was used to compare the correlation of clinicopathologic parameters with AMFR expression.

3 | RESULTS

3.1 | AMFR expression in a variety of IMPCs

IHC results showed that AMFR protein staining was detected primarily in the cytoplasm in 111 samples of IMPC and 26 samples of CPA paraffin-embedded tissues. ROC curves confirmed that AMFR expression could clearly separate the IMPC and non-IMPC components, with a cut-off score of 19 and an area under the curve (AUC) of 0.601 (Figure 1A, $p = .008$). AMFR expression was elevated in IMPC compared to the intrinsic non-IMPC components in lung (Figure 1B,C), breast (Figure 1F,G), urothelial (Figure 1H,I), gastric (Figure 1J,K), and rectum samples (Figure 1L,M). There was no difference in expression in the pancreas (Figure 1N,O) and it was lower in the cervix samples (Figure 1P,Q). Interestingly, hyperexpression of AMFR was also observed in IMPC with tumour emboli in the lymph-vessels (Figure 1D). AMFR expression was elevated in the IMPC and non-IMPC carcinoma components, compared to the normal alveoli in lung samples (Figure 1E).

3.2 | Quantitative analysis of AMFR expression in different components

As shown in Figure 2A, AMFR expression was significantly elevated in the IMPC samples compared to the non-IMPC samples of all 137 cases ($p = .005$). AMFR was elevated in the IMPC and non-IMPC lung carcinoma components compared to the normal alveoli ($p < .0001$). AMFR expression was also higher in the IMPC samples than in the intrinsic non-IMPC components ($p = .0234$) in the 111 cases of IMPC. (Figure 2B) Between the 69 cases of lung IMPC and 26 cases of CPA, AMFR expression was much higher in the IMPC components than in the CPA components ($p = .0455$) (Figure 2C), but no significant difference was found between the non-IMPC components in the lung and the CPA components ($p = .4584$) (Figure 2D). Moreover, elevated AMFR expression was not significantly correlated with the mixed type ($n = 100$) or pure type ($n = 11$) IMPC ($p = .5969$) (Figure 2E). AMFR expression was also not significantly correlated with lymph node status, metastasis or non-metastasis ($p = .9243$) (Figure 2F, Table 2).

3.3 | The correlation of clinicopathologic features with AMFR expression in IMPC

We analysed the correlation between the clinicopathologic features of IMPC with AMFR expression, results are shown in Table 2. In the 111 cases of IMPC, high AMFR expression was not correlated with patient age, gender, T stage, or LNM. Based on the histologic features of lung adenocarcinoma in the 69 cases of lung IMPC, high AMFR expression was not correlated with the location of IMPC, including alveolar or acinus, the mesenchyme, or in both sites ($p = .2768$). We also concluded that the location of IMPC was not correlated with LNM. In lung adenocarcinoma, some cases exhibited mucinous production, which is one of the features

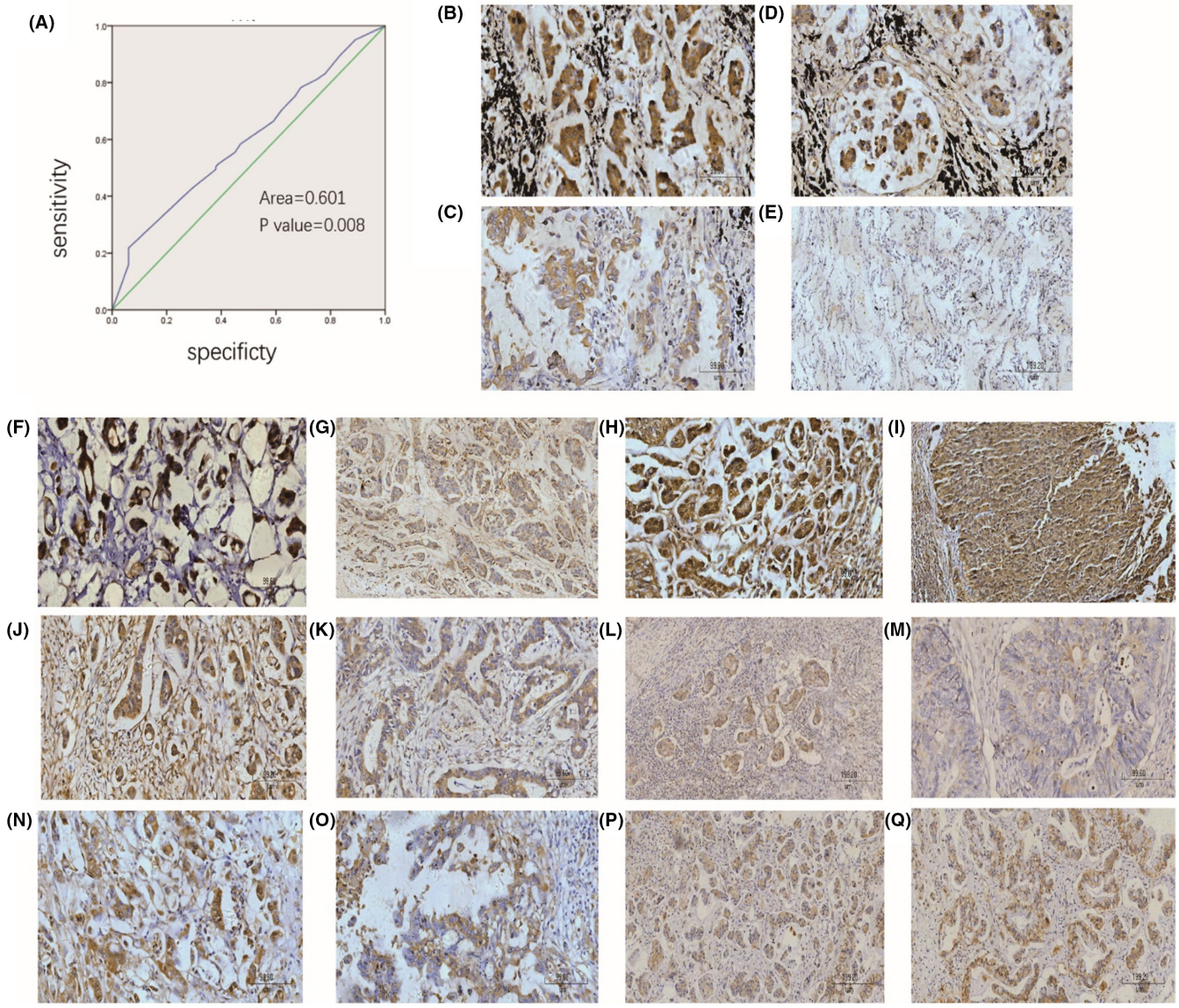

FIGURE 1 AMFR expression in a variety of IMPCs. (A) ROC curves confirmed that AMFR expression clearly separated IMPC and non-IMPC components, with a cut-off score of 19 based on IHC and an area under the curve (AUC) of 0.601, $p = .008$. (B–Q) AMFR expression was mainly elevated in IMPC compared to the intrinsic non-micropapillary components and alveoli in lung (B, C, E), breast (F, G), urothelial (H, I), gastric (J, K), and rectum (L, M). Expression was the same in pancreas (N, O) and lower in cervix (P, Q). Hyperexpression of AMFR was also observed in IMPC with tumour emboli in the lymph-vessels (D).

of adenocarcinoma, but this was not correlated with AMFR expression ($p = .942$).

3.4 | The clinicopathologic features of lung IMPC and CPA

Between IMPC and CPA in the lung (Table 3), there was no significant difference in age, T stage, and LNM. However, AMFR expression was much higher in the IMPC components than in the CPA components ($p = .0071$). In IMPC patients, there was no gender difference, however the CPA patients were predominantly female ($p = .0499$).

3.5 | The clinicopathologic features of mixed and pure type breast IMPC

In the breast samples, there was no significant difference in age, gender, T stage, LNM, or AMFR expression between the mixed type and pure type IMPC (Table 4). In the pure type IMPC, all patients had LNM, which was meaningful and required further sample validation. It is interesting to note that the nuclear grade IMPC components were correlated almost the same with the non-IMPC components in the mixed type breast IMPC. In the 24 cases of mixed type IMPC, there were 5 cases of nuclear grade 3 and 19 cases of grade 2 in the IMPC and

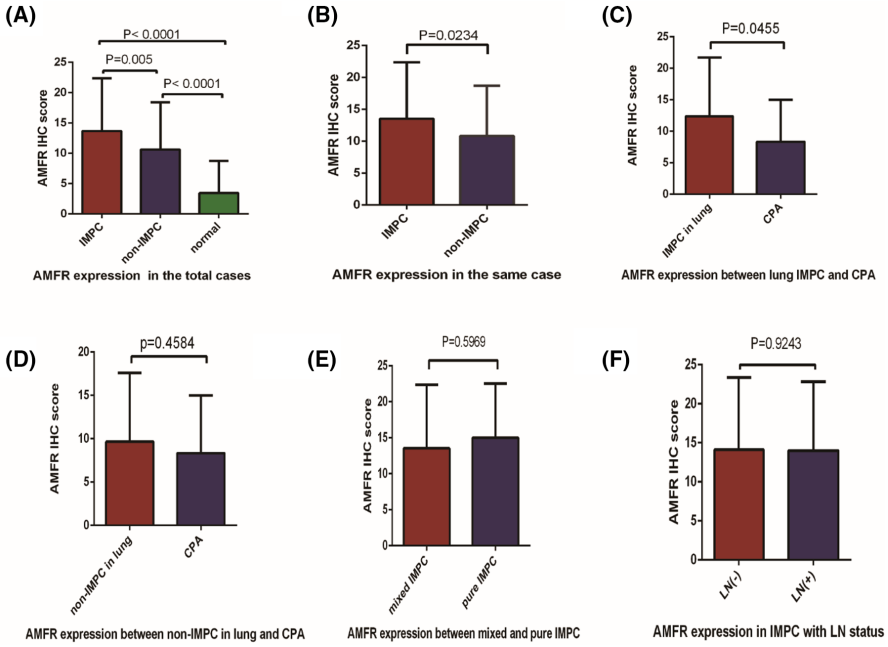

FIGURE 2 Quantitative analysis of AMFR expression in different components. (A) AMFR expression was significantly elevated in IMPC compared to non-IMPC components and normal tissues ($N = 137$). (B) AMFR expression was also higher in the IMPC than in the intrinsic non-IMPC. (C) AMFR expression was significantly higher in IMPC compared to CPA (lung IMPC = 69 cases, CPA = 26 cases). (D) There was no significant difference between non-IMPC components in the lung and CPA components. (E) Elevated AMFR expression was not significantly correlated with mixed type or pure type breast IMPC. (F) Elevated AMFR expression was not significantly correlated with LNM.

TABLE 2 The correlation of clinicopathologic features with AMFR expression in the IMPC

	AMFR high	AMFR low	*p* value
Age			.8301
<50	8	27	
≥50	16	60	
Gender			.9176
Male	11	32	
Female	13	36	
T stage			.488
T1	14	40	
≥T2	10	44	
LN			.9712
M	16	57	
Non-M	8	28	
Pulmonary IMPC location			.2768
Alveolar or acinus	11	41	
Mesenchyme	2	8	
Both sites	3	3	
Mucinous producing in pulmonary IMPC			.942
+	4	6	
–	12	19	

TABLE 3 The clinicopathologic features of pulmonary IMPC and CPA

	IMPC	CPA	*p* value
Age			.3211
<50	14	3	
≥50	55	23	
Gender			.0499
Male	34	7	
Female	35	19	
Mucinous producing			.7087
+	10	3	
–	59	23	
T stage			.1247
T1	39	17	
≥T2	27	5	
LN			.2765
Metastasis	43	13	
Non-metastasis	26	13	
AMFR expression			.0378
High	16	1	
Low	53	23	

non-IMPC components respectively. Nuclear grade was diagnosed according to the semi-quantitative method for assessing histological grade in breast tumours described

TABLE 4 The clinicopathologic features of breast IMPC

	Mixed type	Pure type	*p* value
Age			.6626
<50	14	6	
≥50	10	3	
Gender			1
Male	0	0	
Female	24	9	
T stage			.2006
T1	10	6	
≥T2	14	3	
LN			.068
Metastasis	17	9	
Non-metastasis	7	0	
AMFR expression			.7125
High	4	2	
Low	20	7	

in the WHO classification of the breast. The scores for nuclear atypia (1–3, where 1 represents mild atypia and 3 represents severe atypia) and mitotic count score (1–3, where 1 represents lower proliferative activity and 3 represents higher) were added. A sum of 2–3 represented nuclear grade 1, 4 represented grade 2, and 5–6 represented grade 3.

4 | DISCUSSION

Most cases of IMPC typically result in a poor prognosis with a greater risk of nodal metastases in comparison with corresponding conventional carcinoma.[1,8–16] However, in the ovary, micropapillary carcinoma has been placed in the category of low-grade serous carcinoma.[21] The micropapillary variant of mucinous breast cancer has been associated with a poorer prognosis and a greater occurrence of Her2 overexpression compared with pure mucinous cancer,[22,23] but it exhibits more favourable histological features and survival than IMPC.[23,24] A recent retrospective study[25] examined the prognostic difference between IMPC and IDC. The authors analysed 327 cases of IMPC and 4979 IDC cases that underwent primary resection in their institution between 2008 and 2012. Survival analysis demonstrated no statistically significant difference between IMPC and IDC, indicating that proactive or radical clinical therapy is unnecessary. In the 24 cases of mixed type breast IMPC in the current study, we found that the nuclear grade IMPC components were almost identical to the non-IMPC components, indicating the two components share the same origin. A recent meta-analysis of seven studies showed that the presence of a micropapillary component at radical cystectomy (RC) was not associated with worse recurrence-free, cancer-specific, or overall survival compared with patients with pure urothelial carcinoma (UC).[26] This issue is problematic because many clinicians advise early cystectomy for this disease, even in the absence of invasion into the muscularis propria.[27]

In colorectal cancer, clinical presentation of micropapillary adenocarcinoma (MPA) is more frequent in patients between the ages of 53 and 72,[28] while it is rare in young patients.[29] In the 111 cases of IMPC, the average age was 53.7 years old, which is consistent with the literature.

IMPC is different from papillary carcinoma as it has no fibrovascular core and is thus considered essentially hypovascular. MPCs are known to upregulate the glucose transporter 1 (GLUT1) via the activation of a transcription factor, hypoxia-inducible factor (HIF)-1.[30] IMPC may be associated with the upregulation of several nutrient transporters, ASCT1, ASCT2, GLUT1, and GLUT2, which can contribute to malignant potential by supporting the survival of cancer cells.[30] MUC21D high expressors have a significantly higher proportion of micropapillary elements and a high incidence of lymphatic channel invasion, lymph node metastasis, and recurrence rates.[31] EGFR mutations are frequent in lung adenocarcinoma with a micropapillary component (PA-MPC).[32] Molecular Genotype MPA in colorectal cancer shows frequent TP53, KRAS, and BRAF-V600E mutations, which develop via classical chromosomal instability (CIN pattern) and infrequently via MSI.[5,28] However, whether faulty molecular expression and/or clinicopathological features may lead to poorer prognosis of IMPC remains controversial.

Previously, we found via bioinformatics methods using the Gene Expression Omnibus (GEO) database that the expression of AMFR is significantly increased in BC IMPC. AMFR was originally named gp78 after a glycoprotein of 78 kDa purified from metastatic B16-F1 melanoma cells.[33,34] It was subsequently identified as the receptor for AMF/PGI and named AMFR.[35,36] In the literature, the receptor is referred to as both gp78 and AMFR.

AMFR, like its ligand, has multiple roles dictated by its cellular localization. At the cell surface, AMFR is a cytokine receptor that stimulates cell motility upon AMF/PGI activation. It is also localized to an intracellular mitochondria-associated smooth ER domain where it functions as an E3 ubiquitin ligase. AMFR function, as both cytokine receptor and ubiquitin ligase, is linked to metastasis development and increased invasiveness.[37]

We demonstrated that AMFR expression was significantly elevated in IMPC compared to intrinsic non-IMPC components. In the lung, AMFR expression was much higher in IMPC than in CPA, where no significant difference was observed between the non-IMPC components and the CPA components. The high expression of AMFR in IMPC further confirms that IMPC is prone to metastasis. However, high AMFR expression was not verified to be corelated with LNM in our cases. More cases are needed to confirm these results.

Nakamori et al.[38] found that the overall 5-year survival of patients with AMFR over-expressing colorectal cancers was significantly shorter than in patients that did not over-express AMFR. They did not specifically evaluate the prognostic significance of colon and rectal cancer AMFR expression separately. Recent tissue microarray analysis (TMA) of separate cohorts of colon and rectal cancers unexpectedly showed that AMFR expression was associated with improved patient survival in colon cancer, but with a worse prognosis in rectal cancer[39] The reason behind the difference in clinical significance of AMFR expression for these 2 different lower gastrointestinal cancer types remains unknown. The result may have been due to the small patient population and short duration of clinical follow-up. Future study in a larger colon and rectal cancer patient population with a longer post-treatment follow-up is necessary.[39] Interestingly, an AMFR knockout mouse developed spontaneous liver and colon cancers, suggesting that AMFR may play a tumour suppressor role in these cancer types.[40]

In our study cohort, AMFR expression was mainly elevated in IMPC compared to the intrinsic non-micropapillary components in lung, breast, urothelial, gastric, and rectal cancers. However, expression was the same in cancers of the pancreas and lower cervix. There were only 9 cases of urothelial, gastric, rectal, pancreatic, and cervical IMPC in total. Therefore, more cases are needed to confirm AMFR expression in these organs. The overexpression of AMFR in IMPC further indicates that IMPC is invasive and prone to metastasis.

A monoclonal antibody (mAB) called 3F3A has been used to study gp78/AMFR distribution and its role in cell motility.[35] The 3F3A mAB was also shown to recognize only a subset of total cellular AMFR.[41] This antibody competes with AMF for AMFR binding.[35,42] It is important to recognize that reports of AMFR upregulation in cancer using 3F3A staining may not necessarily reflect increased total AMFR expression, but rather selective upregulation of an active form of the receptor. This may further complicate comparisons of AMFR mRNA expression in studies using the 3F3A mAB.[17] Further investigation into 3F3A immunostaining and comparison with the AMFR results is needed.

The molecular and physiologic properties of AMFR identify it as an attractive therapeutic target compared with other cell surface tumour markers, and its role in metastasis and tumorigenicity makes it a promising functional target. Furthermore, its potential as a molecular target for therapy is enhanced by studies that have reported that AMFR is expressed by tumour cells but has minimal or no expression in adjacent normal tissues of the lung, oesophagus, stomach, colon, skin, bladder, and liver. The ligand of AMFR also offers an advantage as a potential carrier protein in the construction of chemotoxins. The development of anticancer agents that target AMFR, and the use of AMF as a vehicle for the delivery of chemotoxins, may represent novel future treatments for individuals who are diagnosed with cancer.[17]

Li et al.[43] found that POLE mutation is a vital factor in endometrial cancer patients, leading to a higher expression of AMF/PGI and AMFR/gp78. These results suggest that comprehensive consideration of POLE mutations and expression of AMF/PGI and AMFR/gp78 may provide a more feasible and effective approach for the treatment of endometrial cancer and may improve prognosis.

Liver-specific gp78/AMFR genetic ablation resulted in functional protein stabilization of several hepatic P450s and consequently enhanced drug and prodrug metabolism, a feature that could be therapeutically exploited in the bioactivation of chemotherapeutic prodrugs through design and development of novel short-term gp78/AMFR chemical inhibitors.[44] GP78 stimulates ERK activation via DUSP1 degradation to mediate EGFR-dependent cancer cell proliferation and invasion.[45]

5 | CONCLUSION

IMPC has been shown to be metastatic and invasive. Our study found that AMFR was upregulated in a variety of human IMPCs compared with their non-micropapillary components, suggesting a potential new prognostic indicator or therapeutic target for human IMPC.

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CONFLICT OF INTEREST

The authors declared no conflicts of interests.

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