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The clinicopathological and prognostic characteristics of mucinous micropapillary carcinoma of the breast

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Summary. Background. Mucinous micropapillary carcinoma (MMPC) is a unique subtype of breast cancer, and there is as yet no detailed report on the clinical characteristics of MMPC.

Methods. MMPC, pure mucinous breast carcinoma (PMBC), and invasive micropapillary carcinoma (IMPC) samples were enrolled simultaneously, and immunohistochemistry analysis was performed to explore the clinicopathological attributes of MMPC. Moreover, survival analyses of MMPC were performed among the MMPC, PMBC, and IMPC groups and within the MMPC group.

Results. The results showed that MMPC demonstrated distinct pathological features and that vascular invasion and lymph node metastasis were two significant clinical attributes of MMPC. MMPC leads to a shorter survival time than PMBC but an increased survival time compared to IMPC, while the tumor-node-metastasis stage and lymph node metastasis were identified as two independent prognostic elements for disease-free survival in discerning the MMPC prognosis.

Conclusions. The gathered data implied that further understanding and classification of MMPC may provide better individualized therapeutic strategies for MMPC treatment.

Key words: Immunohistochemistry, MMPC, Breast cancer, Prognosis, Pathology

Introduction

Breast cancer (BC) is the most common cancer among women worldwide (Siegel et al., 2019). Making efforts to further understand the histological heterogeneity is of great importance for the diagnosis and treatment of BC. Mucinous carcinoma (MC) is a rare and special subtype of BC with a favorable prognosis that is described as "clusters of generally small and uniform cells floating in large amounts of extracellular mucin" according to the World Health Organization's 2012 breast tumor classification scheme (Pareja et al., 2019; Xu et al., 2019; Marrazzo et al., 2020). Traditionally, MC of the breast consists of the following two subtypes based on the composition of the MC component in the total tumor volume: pure mucinous breast carcinoma (PMBC) (presenting as >90% mucinous component in the tumor) and mixed mucinous breast carcinoma (Bae et al., 2011; Limaiem and Ahmad, 2020).

Early in 2002, Ng (2002) first reported on PMBC with a micropapillary shape consisting of morula-like clusters dangled in tight mucin pools, which was identified as a new subtype of PMBC and designated as mucinous micropapillary carcinoma (MMPC). However, some studies have argued that the arrangement of MMPC is analogous to that of invasive micropapollary carcinoma (IMPC). Moreover, MMPC also tended to correlate with aggressive tumor behaviors, including lymph node metastasis and lymphovascular invasion. Therefore, perhaps MMPC should be categorized as a subtype of IMPC (Chen et al. 2014; Collins and Ricci, 2018). However, because of the rarity of MMPC cases in clinical practice, the classification of MMPC remains disputed.

In this present study, we enrolled MMPC, PMBC, and IMPC samples and explored the clinicopathological characteristics of MMPC, especially the prognostic factors, both among groups and within the MMPC group.

Materials and methods

Sample collection

A total of 40 cases of MMPC were collected from the Department of Pathology of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University from January 2010 to December 2018. Simultaneously, 90 cases of PMBC and 60 cases of IMPC were enrolled as control groups. Important clinicopathologic parameters, including age, menstrual status, tumor size, ultrasound and molybdenum target

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mammography, LVI, LNM, ER, PR, HER2, Ki-67 status, and tumor-node-metastasis (TNM) stage were collected. Moreover, various therapeutic strategies, such as surgical style, adjuvant chemotherapy, radiation therapy, endocrine therapy, and trastuzumab therapy, were also recorded. Each case of BC was diagnosed and classified according to the American Joint Committee on Cancer/International Union against Cancer TNM staging system. Discordant diagnoses of MMPC were reviewed by three pathologists independently using slides immunostained with EMA and MUC1 for consensus (Sun et al., 2020). All cases were carefully followed up with for between two and 118 months (median, 60 months). Written informed consent was acquired from each patient in this study, and the study protocol was approved by the Human Research Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University ([2019]KY083-01).

Immunohistochemistry (IHC) analysis

All tissue wax blocks were fixed with 10% formalin, cut into 4-μm sections, deparaffinized, and rehydrated using graded alcohols. Endogenous peroxidase activity was blocked by incubation in 3% H_2O_2. Antigen retrieval was performed with citrate buffer and microwave heat induction. IHC analysis was conducted as previously described (Mao et al., 2019a,b). All antibodies used for IHC assay are listed in Table 1. Positive ER/PR staining was defined as at least 1% cell nuclear staining, while positive HER2 staining was defined as at least 3+ cell membrane staining or at least 1+ fluorescence in situ hybridization (PathVysion HER2 DNA probe kit). A high proliferation index Ki-67 result was defined as at least 14% cell nuclear staining. Positive staining of neuroendocrine marker Syn, mucin marker MUC2, and EMA and MUC1 was defined by at least 10% cell cytoplasm staining.

Table 1. Antibody details for IHC analysis.

Marker	Information
ER	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
PR	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
HER-2	Roche (Basel, Switzerland), 1:1000
Ki-67	MXB Biotechnology (Fuzhou, China), 1:1000
EMA	MXB Biotechnology (Fuzhou, China), 1:1000
MUC1	MXB Biotechnology (Fuzhou, China), 1:1000
MUC2	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
Syn	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000
CgA	Zhongshan Golden Bridge Biotechnology (Beijing, China), 1:1000

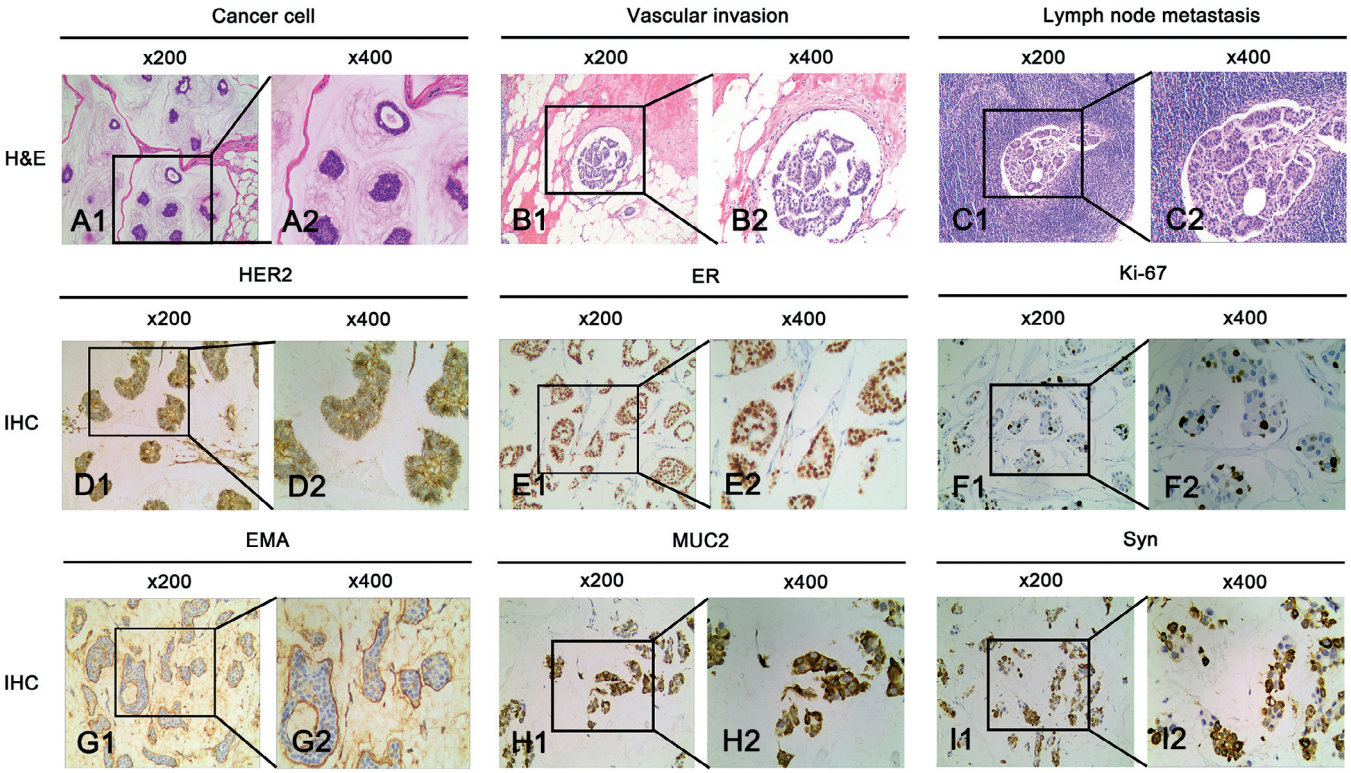

Fig. 1. Representative H&E staining (A-C) and markers IHC staining (D-I) of MMPC samples. **A1, A2.** cancer cell of MMPC. **B1, B2.** vascular invasion of MMPC. **C1, C2.** lymph node metastasis of MMPC. **D1, D2.** Positive staining of HER2 of MMPC. **E1, E2.** Positive staining of ER of MMPC. **F1, F2.** Positive staining of Ki-67 of MMPC. **G1, G2.** Positive staining of EMA of MMPC. **H1, H2.** Positive staining of MUC2 of MMPC. **I1, I2.** Positive staining of Syn of MMPC. A1, B1, C1, D1, E1, F1, G1, H1, I1, × 200; A2, B2, C2, D2, E2, F2, G2, H2, I2, × 400.

Pathological diagnosis of MMPC

The pathological diagnosis of MMPC was required meet the following items concurrently: (1) tumor cells appear in a micropapillary type, pseudo-glandular type, or solid cell-mass cluster type arrangement; (2) mucus fills the contraction spaces around tumor cells; (3) the mucus component accounts for 30% to 90% of the total tumor volume; and (4) EMA/MUC1 demonstrates an "inside-out" staining pattern (Ha et al., 2013; Asano et al., 2019).

Statistical analysis

The data are expressed as mean ± standard deviation values. Differences between two groups were statistically analyzed using Student's t-test. The variables between groups were evaluated using the chi-squared test or Fisher's exact test. Overall survival (OS) and disease-free survival (DFS) curves were drawn using the Kaplan-Meier method and were compared with the log-rank test. Univariate and multivariate Cox regression models were employed to identify the prognostic elements. For all tests, the significance level for statistical analysis was set at $P<0.05$. All data were analyzed using the Statistical Package for the Social Sciences version 23.0 (SPSS Inc., Chicago, IL, USA) and STATA version16.0 (Stata Corporation, College Station, TX, USA) software programs.

Results

Histological morphology of MMPC

MMPC contains a large amount of extracellular mucus (35%-90%). Tumor cells float in the mucous pool in the form of an avascular axis with a micropapillae, morula, or rosette type, and the cubic or columnar cytoplasm is substantial. Representative micropapillae of MMPC can be characterized by a solid cluster or ring arrangement of tumor cells separated by empty space and demonstrated an "inside-out pattern," which can be revealed by staining by EMA or MUC1 (Fig. 1).

Clinicopathologic information of MMPC patients

A total of 40 MMPC samples were collected from women, and the principal clinical data are summarized in Table 2. The mean age of all patients was 56.2 years, and the average tumor diameter was 1.9 cm (range, 1.0-4.5 cm). Six cases had a family history of malignancy (BC or another tumor). There were six cases diagnosed before menopause and 34 cases diagnosed after menopause. Bursting pain during menstruation was noted in 29 patients, and a BI-RADS 4 to 6 level was witnessed in 32 cases by ultrasound and molybdenum target tests. Thirty patients underwent breast-conserving surgery, and 10 underwent modified radical mastectomy. Positive lymph node metastasis and vascular tumor thrombus were observed in 12 and 15 cases, respectively. The numbers of positive expressions of ER, PR, HER2, and Ki-67 were 34, 32, five, and 10, respectively. Molecular classifications were as follows: 24 cases were luminal A, 10 cases were luminal B, three cases were Her2-enriched, and three cases were basal. Positive Syn and MUC2 staining were witnessed in 16 and 23 cases, respectively. All 40 patients underwent postoperative chemotherapy (taxol + platinum), 32 received endocrinotherapy, 12 received radiotherapy, and four received herceptin therapy. Among all cases, 14 patients suffered tumor progression with lymph nodes metastasis to the ipsilateral chest wall, ipsilateral

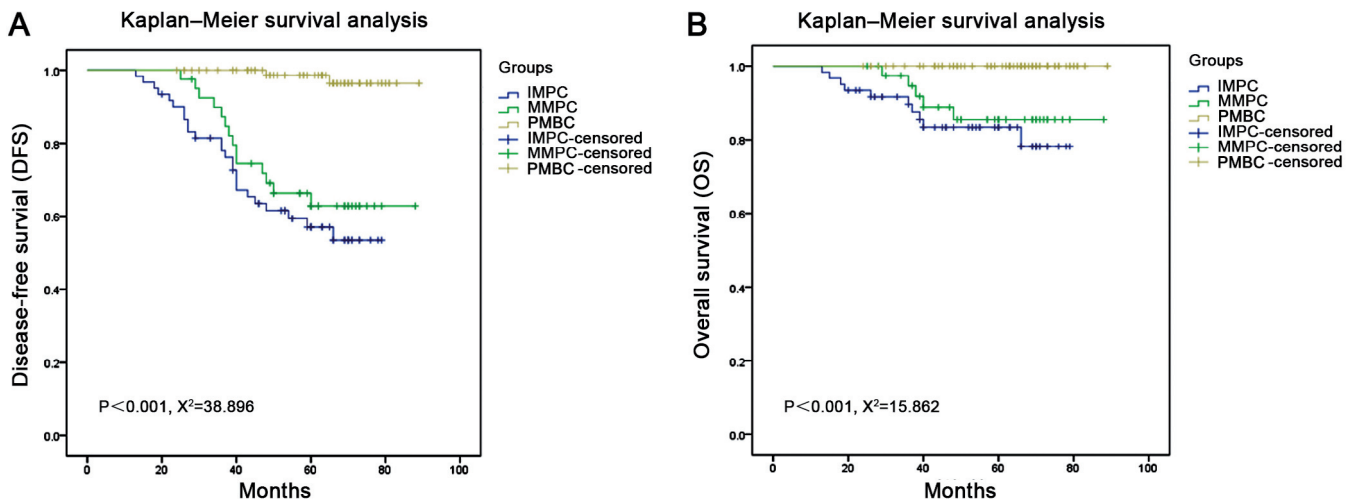

Fig. 2. Survival analysis of MMPC, IMPC and PMBC patients by Kaplan-Meier method. **A.** Disease-free survival (DFS) in patients of MMPC (green line) was significantly lower than that in patients of PMBC (yellow line), while higher than that in patients of IMPC (blue line). **B.** Overall survival (OS) in patients of MMPC (green line) was significantly lower than that in patients of PMBC (yellow line), while higher than that in patients of IMPC (blue line).

Table 2. Comparison of clinicopathological features of MMPC, IMPC and PMBC.

Clinicopathological factors	MMPC (n=40)	PMBC (n=90)	P	MMPC (n=40)	IMPC (n=60)	P
Age (years)			0.565			0.190
≥50	27	61		27	34	
<50	13	29		13	26	
Family history			0.228			0.422
Yes	6	8		6	7	
No	34	82		34	53	
Menstrual state			0.107			0.033*
Postmenopausal	34	66		34	40	
Premenopausal	6	24		6	20	
Ultrasound (BI-RADS grading)			0.001*			0.195
Grade 1-3	8	42		8	7	
Grade 4-6	32	43		32	53	
Molybdenum target (BI-RADS classification)			0.111			0.195
Grade 1-3	8	29		8	7	
Grade 4-6	32	61		32	53	
Adjuvant chemotherapy			0.001*			0.212
Yes	40	72		40	57	
No	0	18		0	3	
Endocrine therapy			0.199			0.524
Yes	32	64		32	47	
No	8	26		8	13	
Herceptin therapy			0.031*			0.341
Yes	4	16		4	9	
No	36	74		36	51	
Radiotherapy			0.219			0.002*
Yes	5	6		5	21	
No	35	84		35	39	
Operation mode			0.512			0.048*
Breast conserving surgery	30	66		30	34	
Modified radical mastectomy	10	24		10	26	
Tumor diameter			0.023*			0.266
≥2cm	22	31		22	38	
<2cm	18	59		18	22	
TNM staging			0.074			0.194
Stage I - II	25	69		25	31	
Stage I - II	15	21		15	29	
Vascular invasion			0.006*			0.012*
Yes	12	9		12	33	
No	28	81		28	27	
Lymph node metastasis			0.001*			0.047*
Yes	15	11		15	34	
No	25	79		25	26	
Neuroendocrine markers (Syn)			0.016*			0.518
Positive	16	18		16	25	
Negative	24	72		24	35	
Mucin labeling (MUC2)			0.118			0.001*
Positive	23	63		23	6	
Negative	17	27		17	54	
Molecular type			0.076			0.001*
Luminal A	24	55		24	13	
Luminal B	10	32		10	31	
HER-2 overexpression	3	2		3	9	
Triple negative	3	1		3	7	
ER expression			0.498			0.287
Positive	34	78		34	47	
Negative	6	12		6	13	
PR expression			0.486			0.019*
Positive	32	70		32	35	
Negative	8	20		8	25	
HER-2 expression			0.058			0.242
0-2+	35	87		35	48	
3+ or FISH+	5	3		5	12	
Ki-67 expression			0.072			0.001*
≥14%	10	36		10	43	
<14%	30	54		30	17	

*p<0.05.

axillary, and supraclavicular area. For TNM stage, 25 patients were in stages I or II, while the other 15 patients were in advanced stages III or IV.

Comparison of clinicopathological parameters between MMPC, PMBC, and IMPC groups

As shown in Table 2, several characteristics were significantly different between the MMPC, PMBC, and IMPC groups. For comparison between the MMPC and PMBC groups, important factors included ultrasound grade, tumor diameter, vascular invasion, lymph node metastasis, and status of Syn. For comparison between the MMPC and IMBC groups, critical attributes included menstruation status, vascular invasion, lymph node metastasis, status of MUC2, molecular type, and PR and Ki-67 statuses. Specifically, vascular invasion and lymph node metastasis were two collective parameters noted when comparing MMPC, PMBC, and IMPC (Table 2).

Survival analysis of MMPC

During comparisons among groups, the one-, three-, and five-year DFS rates of MMPC, PMBC, and IMPC were 100% vs. 100% vs. 100%, 87% vs. 100% vs. 78%, and 62% vs. 99% vs. 57%, while the related one-, three-, and five-year OS rates were 100% vs. 100% vs. 100%, 95% vs. 100% vs. 90%, and 78% vs. 100% vs. 85%. MMPC patients had a shorter survival time than PMBC patients but an increased survival time compared to IMBC patients (Fig. 2). For comparison within the MMPC group for DFS, univariate analysis revealed that tumor diameter, TNM stage, vascular invasion, lymph node metastasis, molecular type, and status of both Ki-67 and Syn could significantly influence MMPC prognosis. Multivariate analysis further confirmed that TNM stage and lymph node metastasis may serve as independent prognostic factors for DFS during MMPC prognosis (Tables 3, 4, Fig. 3).

Discussion

Due to the small number of MMPC cases, most of which are misclassified as PMBC, clinicians and pathologists are far from strongly aware of this type of special BC. The incidence of PMBC of the breast is low,

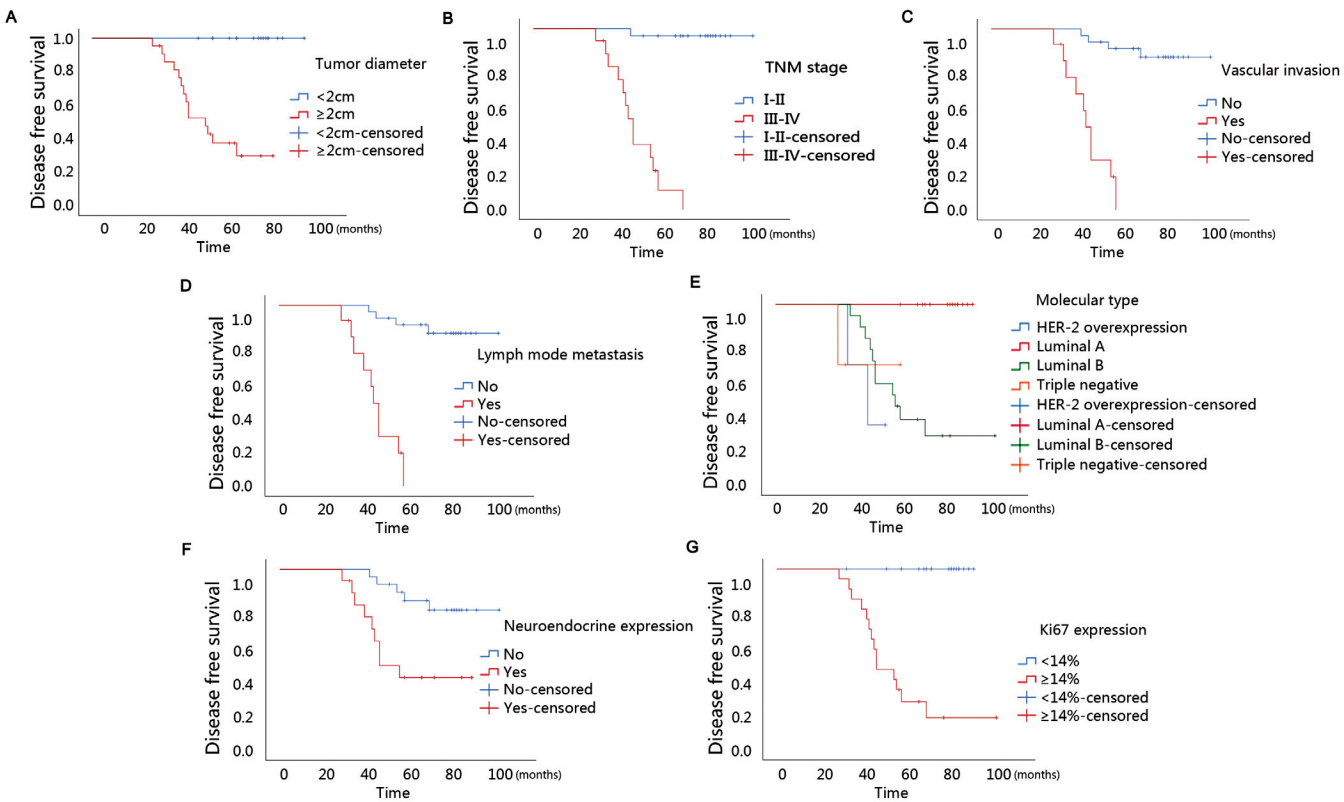

Fig. 3. Survival analysis within MMPC. **A.** Disease-free survival (DFS) in patients with larger tumor diameter (≥2cm) (red line) was significantly lower than that in patients with smaller tumor diameter (<2cm) (blue line). **B.** DFS in patients with III-IV stage (red line) was significantly lower than that in patients with I-II stage (blue line). **C.** DFS in patients with positive vascular invasion (red line) was significantly lower than that in patients with negative vascular invasion (blue line). **D.** DFS in patients with positive lymph node metastasis (red line) was significantly lower than that in patients with negative lymph node metastasis (blue line). **E.** DFS in patients with Luminal B type (green line) was significantly lower than that in patients with Luminal A type (red line), HER2 overexpression type (blue line) and triple negative type (orange line). **F.** DFS in patients with positive neuroendocrine expression (red line) was significantly lower than that in patients with negative neuroendocrine expression (blue line). **G.** DFS in patients with high Ki-67 expression (red line) was significantly lower than that in patients with Ki-67 expression low Ki-67 expression (blue line).

Table 3. Univariate analysis of prognostic factors in MMPC for disease-free survival (DFS).

Parameters	HR	95% CI	P value
Age (years) <50 vs ≥50	0.801	0.340-3.001	0.971
Family history Yes vs No	0.114	0.002-2.154	0.710
Menstrual state Postmenopausal vs Premenopausal	0.321	0.019-3.101	0.812
Ultrasound (BI-RADS grading) Grade 4-6 vs Grade 1-3	3.630	0.123-1.689	0.096
Molybdenum target (BI-RADS classification) Grade 4-6 vs Grade 1-3	3.425	0.173-2.046	0.071
Adjuvant chemotherapy Positive vs Negative	0.362	0.025-3.669	0.968
Radiotherapy Positive vs Negative	1.701	0.641-6.661	0.095
Endocrine therapy Positive vs Negative	0.340	0.056-2.154	0.562
Herceptin therapy Negative vs Positive	1.256	0.684-10.326	0.894
Tumor diameter ≥2cm vs <2cm	17.620	2.697-44.385	<0.001*
TNM stage Stage III-IV vs I-II	28.160	1.621-54.361	<0.001*
Vascular invasion Positive vs Negative	11.365	3.691-30.156	<0.001*
Lymph node metastasis Positive vs Negative	14.700	6.069-22.124	<0.001*
Molecular type Luminal A vs Luminal B HER-2 overexpression vs Triple negative	12.756	6.125-61.578	<0.001*
ER Positive vs Negative	0.140	0.001-6.458	0.710
PR Positive vs Negative	0.364	0.201-6.142	0.698
HER-2 0-2+ vs 3+/Fish+	0.669	0.125-3.458	0.712
Neuroendocrine markers (Syn) Positive vs Negative	5.290	0.175-12.321	0.021*
Mucin labeling (MUC2) Positive vs Negative	0.189	0.001-11.025	0.622
Ki-67 ≥14% vs <14%	26.32	9.187-55.325	<0.001*

*p<0.05.

Table 4. Multivariate analysis of prognostic factors in MMPC for disease-free survival (DFS).

Parameters	95% CI	P value
Tumor diameter ≥2cm vs <2cm	0.643-5.884	0.275
TNM stage Stage III-IV vs I-II	6.083-515.402	0.030*
Vascular invasion Positive vs Negative	0.379-10.761	0.728
Lymph node metastasis Positive vs Negative	1.154-17.298	0.038*
Molecular typing Luminal A vs Luminal B HER-2 overexpression vs Triple negative	0.728-4.442	0.447
Neuroendocrine markers (Syn) Positive vs Negative	0.850-27.533	0.076
Ki-67 ≥14% vs <14%	0.687-38.597	0.926

*p<0.05.

accounting for 1%-4% of invasive BCs. PMBC is more common in elderly women, and the median age of women at the time of PMBC diagnosis is 60 years. As for IMPC, the incidence rate is 1%-8.4%, and the median age at diagnosis is 50 years old. In comparison, the incidence of MMPC is lower (0.1%-0.3%) and the median age at diagnosis tends to be younger compared to those of PMBC and IMPC (Barkley et al., 2008; Di Saverio et al., 2008; Barbashina et al., 2013). In this study, 40 cases of MMPC accounted for 4.76% (40/840 cases) of invasive BCs during the same period. The age at MMPC diagnosis in this population ranged from 30 to 80 years old, and the median age of onset was 57 years old. The above data were in accordance with previous literature.

In terms of histological morphology, the arrangement of MMPC is similar to that of IMPC. The arrangement of tumor cells of MMPC is pseudopapillary or pseudoglandular, and EMA positive staining could be observed on the cell surface facing the surrounding extracellular mucin, and the nuclear grade is mostly medium-high grade. The major difference between MMPC and IMPC is that MMPC tumor cells float in a large amount of mucus, while the key discrepancy between MMPC and PMBC is that PMBC lacks micropapillary structures (Liu et al., 2015; Mercogliano et al., 2017).

Several studies have reported that MC mainly expresses the MUC family of glycoproteins-for example, MUC2, a gel-forming protein-and this is considered to be a barrier to tumor dissemination and makes MC indolent (Matsukita et al., 2003; Garcia-Labastida et al., 2014). This study demonstrated that cases of positive staining in the IPMC, MMPC, and PMBC groups totaled six, 23, and 63 cases, implying that the positive expression of MUC2 in MMPC was similar to that in PMBC. Eswari et al. also described a case of MC of the breast with neuroendocrine-differentiation characteristics (Varadharajan et al., 2015). Meanwhile, Tanuja et al. reported that 40.9% of MMPC cases expressed Syn and chromogranin A (Shet and Chinoy, 2008). In this research, we found that the numbers of positive expressions of Syn among IPMC, MMPC, and PMBC cases were 25, 16, and 18, suggesting that the expression

of neuroendocrine markers in MMPC was similar to that in IMPC.

As for molecular classification, a previous study found that most PMBC cases are the luminal A type, while most IMPC cases are the luminal B type (Gokce et al., 2013). However, studies focusing on the immunophenotyping and molecular classification of MMPC are rare. Barbashina et al. believed that the immunophenotype of MMPC is similar to that of PMBC, with most cases being the luminal A type (Barbashina et al., 2013). In addition, Mercogliano et al. reported positive HER2 overexpression in MMPC (Mercogliano et al., 2017). In this study, the molecular classifications of the 40 MMPC cases were as follows: luminal A type in 24 cases, luminal B type in 10 cases, HER2-overexpression type in three cases, and basal-like type in three cases. These data are in line with the results of previous studies, and MMPC shows unique features intermediate between those of PMBC and IMPC, respectively.

MMPC is relatively rare in clinical practice, and the majority of studies to date have focused on analyzing its pathological attributes while failing to explore prognostic factors. To the best of our knowledge, only Tanuja et al. reported that several elements may affect the OS and DFS of MMPC patients, including histological type, nodal metastases, irregular tumor border, and IMPC type of local recurrence or metastases (Shet and Chinoy, 2008). In this study, we also screened a number of potential prognostic factors, including tumor diameter, TNM stage, vascular invasion, lymph node metastasis, molecular classifications, and statuses of Syn and Ki-67. Overall, TNM stage and lymph node metastasis were two independent prognostic factors of MMPC.

Interestingly, Xu et al. reported that the presence of MMPC was not associated with lymph node metastasis or survival outcome; instead, they asserted that only larger tumor size was significantly correlated with lymph node metastasis (Xu et al., 2019). Our current data are inconsistent with this previous study. Instead, we believe the main reason for this discrepancy may be largely due to two reasons. For one thing, different antibodies were enrolled, as chromogranin A was stained using an antibody from Abcam (Cambridge, England) in the study by Xu et al. but using an antibody from Zhongshan Golden Bridge Biotechnology in our present study. For another, Xu et al. collected 75 cases of MMPC, while we only enrolled 40 patients with MMPC, and our smaller sample size may have led to statistical bias. Future studies that enroll larger MMPC sample numbers are of great importance to confirm or update our present data.

To sum up, as MMPC is a potentially invasive BC with exclusive behaviors, deeply exploring its morphology and biological heterogeneity is extremely critical. In this retrospective study, we enrolled MMPC, PMBC, and IMPC samples simultaneously; compared their clinicopathological characteristics; and identified several possible prognostic factors of MMPC. Our current findings widen the understanding and categorize MMPC more accurately, and they may lead to better individualized therapeutic strategies for MMPC treatment.

Conclusions

MMPC is a distinct subtype of BC, presenting a number of particular characteristics, including prognostic properties. Further understanding and classification of MMPC may provide better individualized therapeutic strategies for MMPC treatment.

Acknowledgements. None.

Conclusions. MMPC is a distinct subtype of breast cancer, which illustrated a number of particular characteristics, including prognostic properties. Further understanding and classification of MMPC may provide better individualized therapeutic strategies for MMPC treatment.

Declarations. Ethics approval and consent to participate

The study protocol was approved by the Human Research Ethics Committee of the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University ([2019]KY083-01).

Consent for publication. Written informed consents were obtained from the patients or family of the patient for publication of this cohort study.

Competing interests. All authors declare that they have no competing financial interests.

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Authors' contributions. XLZ designed the study. YYS, WXG, and GFW collected the tissue samples and clinical data. YYS and WXG performed the IHC analysis. YYS and GFW performed the statistics. YYS drafted the manuscript. XLZ supervised the study. All authors read and approved the final manuscript.

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