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Comparison of clinicopathological characteristics and prognosis among patients with pure invasive ductal carcinoma, invasive ductal carcinoma coexisted with invasive micropapillary carcinoma, and invasive ductal carcinoma coexisted with ductal carcinoma in situ

A retrospective cohort study

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Abstract

This paper aimed to analyze the clinicopathological characteristics of invasive ductal carcinoma with an invasive micropapillary carcinoma component (IDC + IMPC), invasive ductal carcinoma with a ductal carcinoma in situ component (IDC + DCIS), and compare the clinicopathological characteristics and prognosis to those of IDC.

A total of 1713 patients (130 IDC + IMPC cases, 352 IDC + DCIS cases, and 1231 pure IDC cases) who underwent appropriate surgery from June 2011 to September 2017 were retrospectively selected.

Compared to the pure IDC and IDC + DCIS patients, the IDC + IMPC patients presented with more aggressive characteristics, such as a higher proportion of vascular invasion ($P < .001$), fewer progesterone receptor (PR)-positive patients ($P < .001$), a lower proportion of cases in American Joint Committee on Cancer stage I ($P < .001$), a higher recurrence risk ($P < .001$), more deaths ($P < .001$), and more metastatic cases ($P < .001$). Compared to the pure IDC and IDC + IMPC patients, the IDC+DCIS patients presented with less aggressive characteristics, such as a higher proportion of estrogen receptor-positive patients ($P < .001$) and PR-positive patients ($P < .001$), a lower proportion of cases with nerve invasion ($P < .001$) and vascular invasion ($P < .001$), a higher proportion of cases in American Joint Committee on Cancer stage I ($P < .001$), fewer deaths ($P < .001$), and fewer metastatic cases ($P < .001$). The patients with IDC + DCIS had significantly better disease-free survival (DFS) and overall survival (OS) compared to those with pure IDC and IDC + IMPC ($P < .001$). The patients with IDC + IMPC had significantly worse DFS and OS compared to those with pure IDC and IDC + DCIS ($P < .001$). In univariate analysis, the presence of an IMPC component in IDC ($P = .007$), estrogen receptor status ($P = .05$), and PR status ($P = .003$) were factors associated with OS. In multivariate analysis, coexisting IMPC ($P = .04$) was the only independent prognostic factor associated with OS.

Compared to IDC and IDC + DCIS, IDC + IMPC had more aggressive characteristics and significantly worse DFS and OS. Compared to IDC and IDC + IMPC, IDC + DCIS had less aggressive characteristics and significantly better DFS and OS.

Abbreviations: AJCC = American Joint Committee on Cancer, BCS = breast conserving surgery, DCIS = ductal carcinoma in situ, DFS = disease-free survival, DSS = disease-specific survival, EMA = epithelial membrane antigen, ER = estrogen receptor,

Editor: Hisashi Oshiro.

XG and YD authors contribute equally to this clinical research.

This study was approved by Medical Ethics Committee of Jilin Cancer Hospital. The study was conducted in compliance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Due to its retrospective design and anonymous characteristics, the requirement of informed consent from the patients was waived.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors declare no conflicts of interest.

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How to cite this article: Guan X, Xu G, Shi A, Zou Y, Zhan Y, Fan Z, Dong Y. Comparison of clinicopathological characteristics and prognosis among patients with pure invasive ductal carcinoma, invasive ductal carcinoma coexisted with invasive micropapillary carcinoma, and invasive ductal carcinoma coexisted with ductal carcinoma in situ: a retrospective cohort study. Medicine 2020;99:50(e23487).

Received: 13 July 2020 / Received in final form: 30 October 2020 / Accepted: 3 November 2020

http://dx.doi.org/10.1097/MD.0000000000023487

HER2 = human epidermal growth factor receptor 2, IDC = invasive ductal carcinoma, IDC-NST = invasive ductal carcinoma of non-special type, IMPC = invasive micropapillary carcinoma, OS = overall survival, PR = progesterone receptor.

Keywords: breast cancer, clinicopathological characteristics, ductal carcinoma in situ, invasive ductal carcinoma, invasive micropapillary carcinoma, prognosis

1. Introduction

Breast cancer is the most common malignant tumor and the second leading cause of cancer-related mortality in women worldwide.[1,2] Invasive ductal carcinoma (IDC), sometimes called infiltrating ductal carcinoma, is the most common type of breast cancer. About 80% of all breast cancers are IDCs.[3,4] However, some other pathological subtypes can appear in patients with IDC.

Invasive micropapillary carcinoma (IMPC) is a rare pathological subtype accounting for 2% to 8% of invasive breast carcinomas.[5–12] Since Fisher first demonstrated a sample with mulberry morphological changes of invasive papillary carcinoma in 1980,[13] there have been many different reports of IMPC pathological diagnostic standards. The large difference in the reported incidence of IMPC is mainly because, for most cases, IMPC is a component of IDC, and does not represent all components of the cancer. The formal concept of IMPC was initially put forth by Siriaunkgul et al in 1993.[14] Because of its unique morphological characteristics and a higher propensity for invasiveness, IMPC was listed as an independent subtype in the 2003 World Health Organization classification of breast cancer.[15] The typical pathological feature of IMPC is that the tumor cells are arranged in small clusters in the vascular-like interstitial space, and epithelial membrane antigen staining shows cell polarity reversal. Ductal carcinoma in situ (DCIS) is a noninvasive form of breast cancer consisting of malignant cells that do not invade the basement membrane of the breast ducts. The reported percentage of breast cancer patients with DCIS coexisting with IDC varied significantly from 21.3% to 76.9%.[16,17]

IMPC is characterized by multiple lymph node metastases and a higher incidence of vascular invasion (LVI).[14] According to research reports, the lymph node metastasis rate of IMPC is 44% to 85%, much higher than that of non-special type IDC (IDC of non-special type, NST [IDC-NST]), which is about 30%.[8,10,18,19] IMPC is generally considered to have a worse prognosis than IDC. However, some recent observational studies reported that the overall survival (OS) and disease-specific survival of IMPC and IDC were similar.[20,21] For instance, Chen et al[21] and Yu et al[22] found that the OS was similar for IMPC and IDC patients. Chen et al[21] also found that IMPC patients showed a more favorable disease-specific survival compared to IDC patients. However, Shi et al[23] found that the OS and disease-free survival (DFS) were worse in the IMPC group than in the IDC group. DCIS accompanying IDC does not affect systemic treatment, which depends completely on the pathological and molecular characteristics of IDC. Some studies have shown that IDC accompanying DCIS tended to have a favorable histological grade and a better prognosis compared to pure IDC,[24–26] whereas the opposite results have also been demonstrated that the prognosis of IDC coexisting with DCIS compared to pure IDC was not significantly different.[27]

Although it is widely accepted that IMPC presents more aggressive behavior and has a higher incidence of lymph node metastases, IDC coexisting with DCIS tended to have a better survival outcome due to its less biological aggressiveness. However, the prognosis of patients with IDC + IMPC, IDC + DCIS, and pure IDC remains controversial. This study was the first to analyze the breast cancer follow-up database of Jilin Cancer Hospital and conduct a rigorous cohort study of patients with IDC + IMPC, IDC + DCIS, and IDC alone to better understand the clinicopathological characteristics and prognosis of these 3 pathological subtypes and the factors affecting prognosis.

2. Methods

2.1. Case selection, clinical evaluation, and histopathological analysis

The present study is a retrospective cohort study. A total of 130 breast cancer patients with IDC + IMPC, 352 IDC + DCIS patients, and 1231 patients with pure IDC were collected from the follow-up database of the Second Breast Surgery Department of Jilin Cancer Hospital between June 2011 and September 2017. All the patients were female. Histopathological preparations were evaluated by 2 senior independent pathologists who were blinded to clinical outcomes. When the results of the assessment differed, the consensus was reached through discussion and considering the opinion of a third senior pathologist. As the present study is a retrospective study, the histopathological evaluation procedure following the conventional rule. Pathological sections were taken every 0.5 cm apart, along with the maximum tumor diameter. An average of 5 to 6 sections was taken for each breast cancer lesion. IDC + IMPC in our study was defined as the presence of an IMPC component accounting for at least 10% of the entire IDC area. IDC + DCIS in our study was defined as the presence of a DCIS component accounting for at least 10% of the entire IDC area. The definitions of IDC + IMPC and IDC + DCIS for at least a 10% component were based on the proportion of the tumor's maximum cut surface area and the average proportion of the other 4 to 5 sections.

The inclusion criteria were patients:

(1) without neoadjuvant chemotherapy or neoadjuvant endocrine therapy;
(2) who underwent total mastectomy or breast conserving surgery (BCS);
(3) were diagnosed with IDC + IMPC, IDC + DCIS, or IDC alone by paraffin pathology;
(4) with unilateral breast cancer;
(5) tumor stage T1a–T4; and
(6) lymph node stage N1–N3.

The exclusion criteria were:

(1) breast cancer patients who received neoadjuvant chemotherapy or neoadjuvant endocrine therapy;
(2) bilateral breast cancer patients;

(3) patients diagnosed with stage IV breast cancer;
(4) patients with paraffin pathological diagnosis of other types of breast cancer, such as invasive lobular cancer, mucinous cancer, and myeloid cancer;
(5) patients with incomplete clinicopathological data or incomplete follow-up data;
(6) patients had breast malignancy, or other types of malignancies within the last 5 years, except for having cured carcinoma in situ of the cervix.

All cases of IDC + IMPC, IDC + DCIS, and pure IDC that met all of the inclusion criteria and did not meet any of the exclusion criteria were included in the study.

The clinicopathological and prognostic information collected on all patients included age, tumor size, vascular invasion, nerve invasion, lymph node metastasis, tumor stage according to the American Joint Committee on Cancer (AJCC), estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, Ki-67, molecular subtypes, surgical method, adjuvant therapy, date of recurrence or metastasis, survival status, time of death, and causes of death.

2.2. Follow-up

Follow-up was from the day of surgery to the last follow-up (January 30, 2020) or death. DFS was defined as the length of time from surgery to the recurrence of DCIS, invasive breast cancer (local, regional or distant), invasive contralateral breast cancer or second primary malignancy, or death without breast cancer recurrence or second primary malignancy. OS was defined as the length of time from surgery to death from any cause.[28]

2.3. Statistical analysis

The results were analyzed using SPSS version 22.0 (Statistical Package for the Social Sciences Inc., IBM, Armonk, NY). We used the Pearson Chi-squared test to compare the distribution of clinicopathological features between the groups. The Kaplan-Meier method and log-rank test were used to compare DFS and OS. A Cox proportional hazards analysis was used for univariate analysis and multivariate analysis with 95% confidence intervals. A P value $< .05$ was considered statistically significant.

3. Results

3.1. Comparison of clinicopathological characteristics between patients with pure IDC, IDC + IMPC, and IDC + DCIS

A total of 1231 pure IDC cases (71.9%), 130 IDC + IMPC cases (7.6%), and 352 IDC + DCIS cases (20.5%) that met all the inclusion criteria but none of the exclusion criteria between June 2011 and September 2017 were included in this study. There is not any case with a pure IMPC in the IDC + IMPC group. The median age of the entire cohort was 50 years (24–82 years). Most patients were in an earlier stage (44.4% in AJCC stage I, 66.1% in T1, and 59.0% in N0). Most patients had ER-positive (76.7%), PR-positive (64.0%) disease and underwent breast total mastectomy surgery (85.3%). The rate of BCS was 14.7%. The baseline characteristics of the entire cohort and subgroups are summarized in Table 1. Compared to pure IDC patients, the IDC + IMPC patients were older (mean age, 53.0 vs 50.0 years, $P < .001$) and the IDC + DCIS patents were younger (mean age, 48.0 vs 50.0 years, $P < .001$). Compared to the pure IDC and IDC + DCIS patients, the IDC + IMPC patients presented with more aggressive characteristics, such as a higher proportion of vascular invasion (78.9% vs 69.7% vs 50.7%, $P < .001$), less PR-positive patients (56.2% vs 61.6% vs 75.0%, $P < .001$), a trend toward more HER2-positive patients (30% vs 23.2% vs 20.5%, $P = .088$), a lower proportion of cases in AJCC stage I (28.5% vs 44.6% vs 49.7%, $P < .001$), a higher recurrence risk (35.4% vs 20.9% vs 15.7%, $P < .001$), more deaths (20.8% vs 6.0% vs 2.3%, $P < .001$), and more metastatic cases (20.0% vs 8.3% vs 3.1%, $P < .001$). Compared to the pure IDC and IDC + IMPC patients, the IDC + DCIS patients presented with less aggressive characteristics, such as a higher proportion of ER-positive patients (85.2%% vs 82.3% vs 73.7, $P < .001$) and PR-positive patients (75.0% vs 61.6% vs 56.2%, $P < .001$), a lower proportion of cases with nerve invasion (37.1% vs 47.9% vs 53.2%, $P < .001$) and vascular invasion (50.7% vs 60.7% vs 78.9%, $P < .001$), a higher proportion of cases in AJCC stage I (49.7% vs 44.6% vs 28.5%, $P < .001$), fewer deaths (2.3% vs 6.0% vs 20.8%, $P < .001$) and fewer metastatic cases (3.1% vs 8.3% vs 20.0%, $P < .001$). The BCS rate was significantly lower in patients with IDC + DCIS compared to patients with pure IDC (10.8% vs 16.2%, $P = .018$). The comparison between the patients with pure IDC, IDC + IMPC, and IDC + DCIS is presented in Table 1.

3.2. Survival outcomes among patients with pure IDC, IDC + IMPC, and IDC + DCIS

The median follow-up period was 46 months (range, 26–65 months). The patients with IDC + DCIS had significantly better DFS and OS compared to those with pure IDC and IDC + IMPC ($P < .001$). The patients with IDC+IMPC had significantly worse DFS and OS compared to those with pure IDC and IDC + DCIS ($P < .001$) (Fig. 1A and B).

3.3. Univariate and multivariate analysis

Table 2 shows the results of univariate and multivariate analysis. In univariate analysis, the presence of an IMPC component in IDC ($P = .007$), ER status ($P = .050$), and PR status ($P = .003$) were factors associated with OS. In multivariate analysis, the presence of coexisting IMPC ($P = .04$) was the only independent prognostic factor associated with OS. However, ER status ($P = .115$) and PR status ($P = .084$) were no longer independent risk factors for OS. This may have been due to the limited number of case events and a longer follow-up period may be required.

4. Discussion

Breast cancer is a heterogeneous, complex disease with a high degree of genetic diversity between tumors and outcomes, which may be influenced by multiple histologic and biologic features. Studies in this area have shown that short-term treatment failure was associated with the biological behavior of different histological subtypes.[29,30] Currently, the coexistence of an IMPC component in IDC and a DCIS component in IDC has no role in determining the prognosis and adjuvant treatment strategies.

IMPC is a rare special subtype of invasive breast carcinoma. Because of its unique morphological characteristics and a higher propensity of invasiveness, IMPC was listed as an independent subtype in the 2003 World Health Organization

Table 1

Clinicopathologic features of the entire study population and the invasive ductal carcinoma, the invasive ductal carcinoma coexisted with invasive micropapillary carcinoma, and the invasive ductal carcinoma coexisted with ductal carcinoma in situ groups.

Variables	Total, *% n = 1713	IDC, *% n = 1231	IDC + IMPC, *% n = 130	IDC + DCIS, *% n = 352	*P*-value
Follow up (d), mean ± SD	1372.32 ± 585.72	1530.42 ± 509.96	1082.41 ± 633.00	926.49 ± 544.635	
Age (years), mean ± SD	50.45 ± 9.81	50.61 ± 9.83	53.38 ± 10.55	48.81 ± 9.16	
Operation method					**.018**
Total mastectomy	1462	1032 (83.8%)	116 (89.2%)	314 (89.2%)	
BCS	251	199 (16.2%)	14 (10.8%)	38 (10.8%)	
ER status					**<.001**
Positive	1314	907 (73.7%)	107 (82.3%)	300 (85.2%)	
Negative	399	324 (26.3%)	23 (17.7%)	52 (14.8%)	
PR status					**<.001**
Positive	1096	758 (61.6%)	73 (56.2%)	264 (75.0%)	
Negative	617	473 (38.4%)	57 (43.8%)	88 (25.0%)	
HER2 status					.088
Positive	396	285 (23.2%)	39 (30.0%)	72 (20.5%)	
Negative	1317	946 (76.8%)	91 (70.0%)	280 (79.5%)	
Ki-67 status					.062
>20%	860	636 (51.7%)	67 (51.5%)	157 (44.6%)	
<20%	853	595 (48.3%)	63 (48.5%)	195 (55.4%)	
Nerve invasion					**<.001**
Yes	494	353 (53.2%)	46 (47.9%)	95 (37.1%)	
No	522	311 (46.8%)	50 (52.1%)	161 (62.9%)	
Vascular invasion					**<.001**
Yes	752	524 (69.7%)	86 (78.9%)	142 (50.7%)	
No	389	228 (30.3%)	23 (21.1%)	138 (49.3%)	
Pathological tumor stage					**.003**
T1 (1a 1b 1c 1mi)	1133	817 (66.4%)	74 (56.9%)	242 (56.9%)	
T2	527	383 (31.1%)	52 (40.0%)	92 (26.1%)	
T3	14	4 (0.3%)	2 (1.5%)	8 (2.3%)	
T4	6	5 (0.4%)	0	1 (0.3%)	
T_X	33	22 (1.8%)	2 (1.5%)	9 (2.6%)	
Pathological lymph node stage					**<.001**
N0 (N0 N0+)	1010	734 (59.4%)	51 (39.2%)	225 (63.9%)	
N1 (N1 N1mi)	543	391 (31.8%)	58 (44.6%)	94 (26.7%)	
N2	109	75 (6.1%)	13 (10.0%)	21 (6.0%)	
N3	49	29 (2.4%)	8 (6.2%)	12 (3.4%)	
Nx	2	2 (0.2%)	0	0	
Pathological stage					**<.001**
I (IA IB)	761	549 (44.6%)	37 (28.5%)	175 (49.7%)	
II (IIA IIB)	666	484 (39.3%)	55 (42.3%)	127 (36.1%)	
IIIA	137	96 (7.8%)	23 (17.7%)	18 (5.1%)	
IIIB	9	7 (0.6%)	1 (0.8%)	1 (0.3%)	
IIIC	108	75 (6.1%)	12 (9.2%)	21 (6.0%)	
Recurrence risk					**<.001**
Low	17	6 (0.5%)	0	11 (3.2%)	
Medium	1321	958 (78.6%)	84 (64.6%)	279 (81.1%)	
High	355	255 (20.9%)	46 (35.4%)	54 (15.7%)	
Death					**<.001**
Yes	109	74 (6.0%)	27 (20.8%)	8 (2.3%)	
No	1604	1157 (94.0%)	103 (79.2%)	344 (97.7%)	
Recurrence					**.006**
Yes	79	69 (5.6%)	4 (3.1%)	6 (1.7%)	
No	1634	1162 (94.4%)	126 (96.9%)	346 (98.3%)	
Metastasis					**<.001**
Yes	139	102 (8.3%)	26 (20.0%)	11 (3.1%)	
No	1574	1129 (91.7%)	104 (80.0%)	341 (96.9%)	
Location of metastasis					
Lung	35	26 (23.9%)	8 (6.2%)	1 (0.3%)	
Lung and liver	1	0	1 (0.8%)	0	
Lung and bone	12	7 (6.4%)	5 (3.8%)	0	
Lung and brain	3	1 (0.9%)	1 (0.8%)	1 (0.3%)	
Liver	21	13 (11.9%)	6 (4.6%)	2 (0.6%)	

(*continued*)

Table 1

(continued).

Variables	Total, *% n = 1713	IDC, *% n = 1231	IDC + IMPC, *% n = 130	IDC + DCIS, *% n = 352	*P*-value
Liver and lung and bone	7	6 (5.5%)	1 (0.8%)	0	
Liver and bone	5	3 (2.8%)	1 (0.8%)	1 (0.3%)	
Bone	32	28 (25.7%)	0	4 (1.1%)	
Others	475	25 (22.9%)	107 (82.3%)	343 (97.4%)	

BCS = breast conserving surgery, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.

classification of breast cancer.[15] Data show that IMPC accounts for 2.0% to 8.0% of all invasive breast carcinomas. In accordance with the current research, the rate of IMPC detection was 7.6% in our study when all breast cancer patients in the follow-up database were evaluated. Almost all of the cases occurred in females, with only a few reported to occur in males.[31] According to the histological type of breast invasive carcinoma, IMPC is divided into 2 types, a simple type and a mixed type. Among them, the most common is IMPC of different proportions coexisting with non-specific-type IDC, and only a few mixed types have been reported to coexist with invasive lobular carcinoma and mucinous carcinoma.[12] All of the tumors in our study with mixed IMPC events (100%) were IDC-NST + IMPC. Fu et al[32] showed that even when the IMPC component in invasive breast carcinoma was less than 10%, its metastatic capacity was significantly higher than that of IMPC-free invasive breast carcinoma. For this reason, IMPC should be diagnosed as long as it is contained in the tumor, and the proportion of IMPC and other histological types should also be illuminated.

IMPC of the mammary gland has a typical morphological structure, which is characterized by polarity reversal. The immunohistochemical characteristic of IMPC is that epithelial membrane antigen is positively expressed on tumor cell nests, micropapillary, and glandular duct surfaces (facing the interstitial side). Badyal et al[33] reported that E-cadherin was strongly expressed on the junction surface of tumor cells in IMPC cell nests, while it was weakly or not expressed on the lateral surface of tumor cells and stroma. This suggests that the tumor cell mass has a strong intercellular binding force, and its growth and even invasion and metastasis capacity, may be carried out in the manner of "collectivization" in the form of micropapillary cancer cells. The tumor cell mass is loosely connected to the stroma, facilitating migration from the primary location, resulting in invasion and metastasis.

IMPC is characterized by multiple lymph node metastases and a higher incidence of vascular invasion (LVI). In the current study, compared to the pure IDC and IDC + DCIS patients, the IDC + IMPC patients presented with more aggressive characteristics, such as a higher proportion of vascular invasion (78.9% vs 69.7% vs 50.7%, $P < .001$), fewer PR-positive patients (56.2% vs 61.6% vs 75.0%, $P < .001$), a trend toward more HER2-positive patients (30% vs 23.2% vs 20.5%, $P = .088$), a lower proportion of cases in AJCC stage I (28.5% vs 44.6% vs 49.7%, $P < .001$), a higher recurrence risk (35.4% vs 20.9% vs 15.7%, $P < .001$), more deaths (20.8% vs 6.0% vs 2.3%, $P < .001$), and more metastatic cases (20.0% vs 8.3% vs 3.1%, $P < .001$). Tang et al[34] demonstrated that IMPC patients had a higher incidence of lymph vascular invasion and axillary lymph node extracapsular extension, and a higher degree of lymph node involvement than IDC patients. Umeda et al[35] found that CD44v6 in the IMPC component and CD44v9 in the IDC-NST component of lymph node metastasis cases were significantly lower compared to cases without lymph node metastasis, indicating that decreased CD44 expression may play an important role in promoting lymph node metastasis in IMPC through an inability or decreased capacity to bind with the surrounding stroma.

Whether IMPC has a worse prognosis than IDC remains controversial. Hao et al[36] demonstrated that the prognosis of patients with IMPC of the breast was not different than that of patients with IDC through a propensity-matched analysis. Chen et al[37] suggested that patients with IMPC of the breast had better long-term survival than patients with IDC despite its aggressive

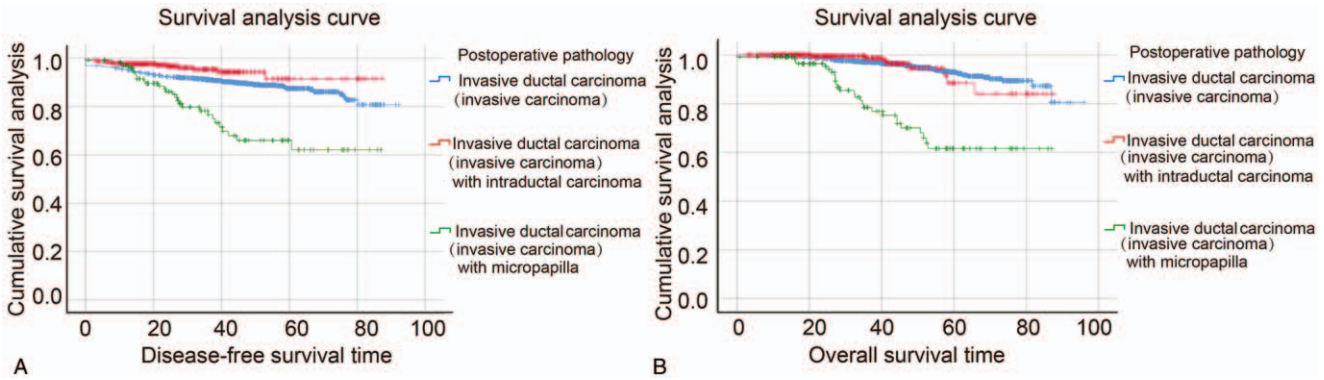

Figure 1. Kaplan–Meier survival curves for the pure invasive ductal carcinoma, the invasive ductal carcinoma coexisted with invasive micropapillary carcinoma, and the invasive ductal carcinoma coexisted with ductal carcinoma in situ patients. (A) Disease-free survival; (B) overall survival.

Table 2

Cox univariate and multivariate regression analysis of risk factors for overall survival.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	0.994	0.976–1.013	.550			
Operation method						
Total mastectomy	1.0		1.0			
BCS	1.053	0.529–2.098	.882			
ER status						
Positive	0.695	0.477–0.954	.050	0.941	0.542–1.235	.115
Negative	1.0		1.0	1.0		1.0
PR status						
Positive	0.540	0.363–0.805	.003	0.605	0.343–1.069	.084
Negative	1.0		1.0	1.0		1.0
HER2 status						
Positive	1.221	0.823–1.810	.321			
Negative	1.0		1.0			
Ki-67 status						
>20%	1.143	0.769–1.699	.508			
<20%	1.0		1.0			
Nerve invasion						
Yes	0.832	0.485–1.427	.504			
No	1.0		1.0			
Vascular invasion						
Yes	0.888	0.476–1.655	.707			
No	1.0		1.0			
Pathological tumor stage						
T1 (1a 1b 1c 1mi)	1.0		1.0			
T2	0.989	0.666–1.469	.957			
T3	0.508	0.070–3.705	.504			
T4	1.254	0.449–3.506	.666			
Pathological lymph node stage						
N0 (N0 N0+)	1.0		1.0			
N1 (N1 N1mi)	0.898	0.486–1.675	.712			
N2	1.035	0.653–1.642	.882			
N3	1.455	0.794–2.667	.225			
Pathological stage						
I (IA IB)	1.0		1.0			
II (IIA IIB)	0.969	0.537–1.749	.918			
IIIA	0.767	0.410–1.436	.407			
IIIB	1.358	0.392–4.700	.629			
IIIC	1.299	0.661–2.553	.448			
Recurrence risk						
Low						
Medium	1.0		1.0			
High	1.140	0.768–1.691	.515			
Pathological type						
IDC	1.0		1.0	1.0		1.0
IDC + IMPC	1.919	1.197–3.077	.007	1.677	1.023–2.749	**.040**
IDC + DCIS	0.886	0.425–1.849	.748	0.841	0.402–1.759	.645

BCS = breast conserving surgery, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.

clinical characteristics, through a comparison based on a large-population database and case-control analysis. Liu et al[38] found that the OS and DFS were worse in the IMPC group than in the IDC group, mainly because β1 integrin overexpression contributed to polarity reversal, leading to a poor prognosis. Our data showed that the IDC + IMPC patients had significantly worse DFS and OS compared to those with pure IDC and IDC + DCIS ($P < .001$). Lewis et al[39] carried out a retrospective analysis and reported that patients of IMPC with triple-negative molecular subtypes had worse OS (hazard ratio 7.28, $P < .001$). Therefore, based on the above reports and our findings, we believe that IMPC is a unique subtype with poor prognosis, and its malignancy is significantly higher than that of patients without an IMPC component.

DCIS is a proven precursor to IDC and often coexists pathologically with IDC.[40] It remains unclear whether the prognosis is similar for IDC when it presents alone or accompanied by DCIS. Some studies demonstrated that IDC + DCIS represented a clinical and biological entity distinct from pure IDC and showed that IDC + DCIS was associated with smaller tumor size, less lymph node metastasis, and well-differentiated histological grade tumors,[25] consistent with the results of our study. Compared to pure IDC and IDC + IMPC patients, the IDC + DCIS patients presented with less aggressive

characteristics, such as a higher proportion of ER-positive patients (85.2%% vs 82.3% vs 73.7, $P < .001$) and PR-positive patients (75.0% vs 61.6% vs 56.2%, $P < .001$), a lower proportion of cases with nerve invasion (37.1% vs 47.9% vs 53.2%, $P < .001$) and vascular invasion (50.7% vs 60.7% vs 78.9%, $P < .001$), a higher proportion of cases in AJCC stage I (49.7% vs 44.6% vs 28.5%, $P < .001$), fewer deaths (2.3% vs 6.0% vs 20.8%, $P < .001$), and fewer metastatic cases (3.1% vs 8.3% vs 20.0%, $P < .001$). The BCS rate was significantly lower in patients with IDC + DCIS compared to patients with pure IDC (10.8% vs 16.2%, $P = .018$). However, Papantoniou et al[27] found that IDC + DCIS was a more aggressive phenotype due to its significantly higher Ki-67 expression compared to pure IDC. Wong et al[41] indicated that Ki-67 was lower in IDC + DCIS than in pure IDC and predicted less biological aggressiveness in lymph node metastasis luminal breast cancer. Chen et al[17] suggested that IDC + DCIS had significantly better survival outcomes than pure IDC probably because of the less aggressive characteristics, and in a matched case-control analysis, the coexistence of DCIS was an independent favorable prognostic factor in ER-positive patients. Chih Wan Goh et al[42] reported that IDC + DCIS patients had more favorable clinicopathological features and better survival outcomes compared to IDC patients. Our study found that the IDC + DCIS patients had significantly better DFS and OS compared to those with pure IDC and IDC + IMPC ($P < .001$).

To our knowledge, the current work was the first and largest single-institution study to analyze the clinicopathological characteristics and clinical prognosis of IDC + IMPC, IDC + DCIS, and pure IDC patients. The advantage of this study was in analyzing the database of our own department that included complete immunohistochemical sections and detailed follow-up information for the patients' clinical assessments. However, this study had several limitations. First, our study was a retrospective analysis, and treatment decisions were affected by pathological reports and patient preference rather than randomization. Second, more patients and longer follow-up periods should be analyzed to identify more significant differences in univariate and multivariate analysis. Finally, as the present study is a retrospective study, the histopathological evaluation procedure following the conventional rule, not a defined study procedure. As an instinct characteristic of observational study, there should be selection bias in the present study. To pursue further, large scale clinical observations and gene expression research are needed to uncover the mechanisms and provide strategies for personalized treatments.

5. Conclusion

In summary, our study was the first to compare the clinicopathological characteristics and prognosis of 3 pathological subtypes, IDC + IMPC, IDC + DCIS, and IDC alone. Compared to IDC and IDC + DCIS, IDC + IMPC had more aggressive characteristics and significantly worse DFS and OS. Moreover, coexisting IMPC tumors were associated with more HER2-positive subtypes and significantly decreased prognosis in this cohort of patients. Compared to IDC and IDC + IMPC, IDC + DCIS had less aggressive characteristics and significantly better DFS and OS. However, gene expression profiling studies and clinical research are essential to explain the biological behavior of IDC with coexisting IMPC, and IDC with coexisting DCIS.

Acknowledgments

The authors acknowledge the Department of Pathology of Jilin Cancer Hospital and First Hospital of Jilin University for tissue processing and pathology diagnosis. Many thanks go to the Medjaden Co. and MogoEdit company for provided professional language editing work for this manuscript. The authors also acknowledge Sufen Qi, School of Mathematics of Jilin University for provided statistical support for this study.

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