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The Clinicopathological Characteristics of Pure and Mixed Invasive Micropapillary Breast Carcinomas: A Single Center Experience

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Background: Invasive micropapillary carcinoma (IMPC) is a rare tumor of the breast. IMPC can be classified as a pure or mixed type based on the extent of micropapillary differentiation.

Aims: To evaluate the prognostic importance of the IMPC component in breast cancer through retrospective comparison of the clinicopathological characteristics and clinical outcomes of pure and mixed IMPC patients.

Study Design: The data of 147 (2.2%) patients with IMPC among 6648 patients histopathologically diagnosed with invasive breast cancer between January 2000-2022 were retrospectively reviewed. The patients were assigned to two groups: pure IMPC and mixed IMPC.

Methods: The clinicopathological features such as age at diagnosis, histological type, grade, size, and components of mixed carcinoma, the numbers of metastatic lymph nodes, presence of lymph vascular invasion, hormone receptor, and the Her-2 status of the tumor, T, N, M stages, and the survival rates were reviewed. The clinicopathologic features, patterns of failures, and survival rates were coded and compared between pure and mixed IMPC patients.

Results: A total of 45 patients (30.6%) had pure and 102 patients (69.4%) had mixed IMPC. The median follow-up time was 46 months (3-178). The progesterone receptor positivity rate was significantly lower in the pure group than in the mixed group (66.7% vs. 83.3%, p: 0.024). In the pure and mixed groups, respectively, the 5-year overall survival was 90% and 91% (p: 0.839); progression-free survival was 70% and 77% (p: 0.537); locoregional recurrence-free survival was 86% and 95% (p: 0.043); 5-year distant metastasis-free survival was 88% and 83% (p: 0.066), and the locoregional recurrence rate was 10.3% and 2% (p: 0.052).

Conclusion: Compared to the mixed IMPC, pure IMPC appears to have a more aggressive behavior with lower locoregional recurrence-free survival and more locoregional recurrences. This may be due to the low progesterone receptor positivity rate.

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INTRODUCTION

Invasive micropapillary carcinoma (IMPC) is a rare breast tumor of frequency 1%-8.4%.[1,2] Pathologically, it has an aggressive nature with a tendency for lymph vascular invasion (LVI) and lymph node (LN) metastasis; therefore, it is assumed to have a worse prognosis than that of infiltrative ductal carcinoma (IDC).[3-5] Several studies in the literature have compared IMPC and IDC in terms of clinicopathological features.[6-12] MPC can be classified as a pure or mixed subtype based on the extent of micropapillary components. When compared with pure IMPC, the mixed subtype is more frequent and includes IDC as the main component. However, only a few studies have evaluated pure and mixed IMPC.[13-15] IMPC has been reported as an independent prognostic factor for breast cancer, stressing the need to apply different treatment modalities. Since it is a rare tumor and the number of patients in the literature is low, there is no consensus on this point.

We aimed to evaluate the prognostic importance of the IMPC component in breast cancer by comparing the clinicopathological characteristics and clinical outcomes between pure and mixed IMPC patients.

MATERIALS AND METHODS

Patient Selection

The data of 147 (2.2%) patients with IMPC among 6,648 patients diagnosed histopathologically with invasive breast cancer between January 2000-2022 were retrospectively reviewed. We assigned the patients into two groups: pure IMPC and mixed IMPC. We considered only tumors that showed micropapillary growth patterns as pure IMPC and those associated with other types of invasive breast cancer as mixed IMPC. In all, pure IMPC was noted in 45 patients (30.6%) and mixed IMPC in 102 patients (69.4%).

The clinicopathological features such as age at diagnosis, histological type, grade, size, and components of mixed carcinoma, the number of metastatic LNs, presence of LVI, hormone receptor, and the Her-2 status of the tumor, T, N, M stages, and survival rates were accordingly reviewed. Histopathological diagnosis was made via excisional biopsy or trucut biopsy. The hormonal subtype was analyzed in 3 groups HR (hormone receptor) (+), Her-2 (human epidermal growth factor receptor) (-), HER2 (+), and Triple (-). Considering AJCC 2018 (American Joint Committee on Cancer, 8th edition), the T, N, and M stages were determined.

Treatment Features

Chemotherapy (CT), hormonotherapy (HT), or both were applied according to the tumor characteristics of the patients. Adjuvant curative radiotherapy (RT) was applied in patients who underwent breast-conserving surgery and in patients with tumors of size > 5 cm and/or LN positivity after mastectomy. The median dose to the chestwall was 50 Gy,to the breast was 60 Gy. In addition, a median total dose of 50 Gy was applied to the regional lymphatics according to the indication status. Patients with bone metastases received 30 Gy of palliative RT.

Statistical Analysis

SPSS version 22 (Chicago, IL) was used. Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to test the conformity of the variables to the normal distribution. Since the numerical variables demonstrated nonnormal distribution, they were given as median (range), while categorical variables were given as absolute values and percentages. The median scores of numerical variables were compared with the nonparametric Mann-Whitney U-test. The proportions of patients with pure and mixed IMPC were presented by categorical variables using crosstabulations. The Chi-square test was used to compare these proportions.The overall survival (OS), progression-free survival (PFS), locoregional recurrence-free survival (LRRFS), and distant metastasis (DM)-free survival (DMFS) were calculated from the diagnosis until the last follow-up or death, to the last follow-up or any event, to the last follow-up or locoregional recurrence and, to the last follow-up or DM, respectively.

We defined locoregional recurrence (LRR) as tumor monitoring in the ipsilateral breast and chestwall, axilla, internal mammary, supra, and infraclavicular lymphatic stations. Metastases on the other sides were defined as DMs. We created survival curves with the Kaplan-Meier method and used the log-rank test for comparisons.

Posthoc power analysis was conducted to evaluate the power of the study. A two-sided log-rank test with an overall sample size of 139 subjects (39 in the pure IMPC group and 100 in the mixed IMPC group) achieved 68.9% power at a 0.050 significance level to detect a statistically significant difference in the LRRFS rates between the patient groups.

RESULTS

Clinicopathologic Characteristics

Our study included 147 (2.2%) patients with IMPC among 6,648 patients histopathologically diagnosed with invasive breast cancer between January 2000-2022. A total of 45 patients (30.6%) had pure and 102 patients (69.4 %) had mixed IMPC. The median age of the patients was 48 (18-83) years. All patients were women. Of these, 73 patients were premenopausal (49.7%), 69 (46.9%) were postmenopausal, and 5 (3.4%) were perimenopausal. Pure and mixed IMPC patients were compared in terms of their age, tumor size, molecular subtypes, T, N, M stage, OS, LRRFS, and DMs. The clinicopathologic features of pure and mixed IMPC cases are summarized in Table 1. The median age was 48 years among pure patients and 49 years among mixed patients (*p*: 0.878). The median tumor size was 2.8 cm in the pure group and 3 cm in the mixed group (*p*: 0.705).

IDC was found in 88 (86.3%) mixed IMPC cases, followed by invasive lobular carcinoma in 15 cases (14.7) and invasive mucinous carcinoma in 10 cases (9.8%). The most common component in mixed IMPC cases was IDC, as the only component in 77 cases (75.5%) and other components in 11 cases (10.8).

TABLE 1. Clinicopathologic Characteristics of Pure and Mixed IMPC Cases

	Pure IMPC (n: 45)	Mixed IMPC (n: 102)	p
	Median (min-max) n (%)	Median (min-max) n (%)	
Age	48 (27-73)	49 (18-83)	0.878
Tumor size	2.8 cm (0.7-10.5)	3 cm (0.4-11)	0.705
Histological grade			
1	1 (2.2)	2 (2)	
2	20 (44.4)	53 (52)	0.703
3	24 (53.3)	47 (46.1)	
ER			
Negative	6 (13.3)	12 (11.8)	0.789
Positive	39 (86.7)	90 (88.2)	
PR			
Negative	15 (33.3)	17 (16.7)	0.024
Positive	30 (66.7)	85 (83.3)	
HER2			
Negative	32 (71.1)	70 (68.6)	0.763
Positive	13 (28.9)	32 (31.4)	
Hormonal subtypes			
HR+HER2-	30 (66.7)	65 (63.7)	
HER2+	13 (28.9)	32 (31.4)	0.942
Triple-	2 (4.4)	5 (4.9)	
LVI			
Negative	14 (31.1)	45 (44.1)	0.138
Positive	31 (68.9)	57 (55.9)	
ECE			
Negative	30 (66.7)	75 (73.5)	0.396
Positive	15 (33.3)	27 (26.5)	
LN metastatis			
Yes	33 (73.3)	65 (63.7)	0.255
No	12 (26.7)	37 (36.3)	
Number of LN metastasis	3 (0-31)	1 (0-31)	0.149
T			
1	16 (35.6)	24 (23.5)	
2	18 (40)	57 (55.9)	0.391
3	5 (11.1)	12 (11.8)	
4	6 (13.3)	9 (8.8)	
N			
0	12 (26.7)	36 (35.3)	
mic	2 (4.4)	4 (3.9)	
1	10 (22.2)	21 (20.6)	0.822
2	10 (22.2)	16 (15.7)	
3	11(24.4)	25 (24.5)	
M			
0	42 (93.3)	89 (87.3)	0.275
1	3 (67)	13 (12.7)	
Chemotherapy			
Yes	39 (86.7)	84 (82.4)	0.514
No	6 (13.3)	18 (17.5)	
Endocrine treament			
Yes	38 (84.4)	90 (88.2)	0.528
No	7 (15.6)	12 (11.8)	
Radiotherapy			
Curative	36 (80)	77 (75.5)	0.709
Palliative	1 (2.2)	5 (4.9)	
None	8 (17.8)	20 (19.6)	

ER, estrogen receptor; PR, progesterone receptor, HR, hormone receptor; Her 2, Human epidermal growth factor receptor 2; LVI, lymphovascular invasion, ECE, extracapsular extension; mic, micrometastasis; min, minimum; max, maximum

The median Ki-67 value was 30 in both groups (*p*: 0.568). There was no difference between the groups in terms of estrogen receptor (ER) and HER2 expression. The progesterone receptor (PR) positivity rate was significantly lower in the pure group than in the mixed group (66.7% vs. 83.3%, *p*: 0.024). Although LVI, extracapsular extension (ECE), LN metastasis, and the number of LN metastases were higher in the pure group, the difference was not statistically significant. The LVI rate was 68.9% in the pure group and 55.9% in the mixed group (*p*: 0.138). The LN metastasis rate was 73.3% in the pure group and 63.7% in the mixed group (*p*: 0.255).

We did not observe any difference between the groups in terms of the T and N stages at the time of diagnosis. Although the rate of patients with DM was higher in the mixed group, this difference was not statistically significant (12.7% vs. 6.7%, *p*: 0.275). There was no difference between the groups regarding RT, CT, and HT.

Comparison of Survival Outcomes and Failure Patterns

The median follow-up time was 46 months (3-178). Six patients without follow-up data were not included in the survival analysis. In the pure and mixed groups, respectively, the 5-year OS was 90% and 91% (*p*: 0.839) (Fig. 1); PFS was 70% and 77% (*p*: 0.537); LRRFS was 86% and 95% (*p*: 0.043); and the 5-year DMFS was 88% and 83% (*p*: 0.066) (Fig. 3). The LRRFS curves of pure and mixed IMPC cases are given in Figure 2 and the survival rates in Table 2.

LRR rate was different in pure and mixed patients. It was 10.3% in pure IMPC patients and 2% in the mixed IMPC group (*p*: 0.052). There was no difference between the groups regarding DM and death with disease rates. The patterns of failure of cases are depicted in Table 3.

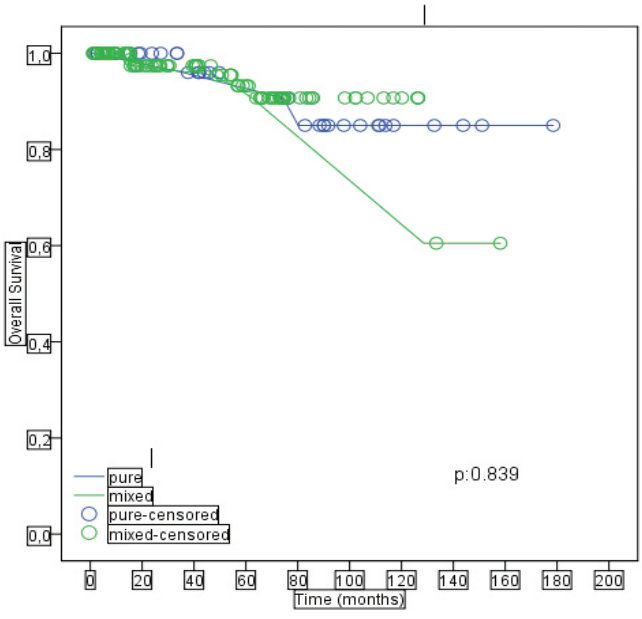

FIG. 1. Overall survival curves of pure and mixed IMPC cases

DISCUSSION

In our study, the incidence of IMPC was 2.2% in total (147/6648). As in the literature, most of the patients (1.5%) had mixed IMPC, whereas only 0.7% had the pure form.[16,17]

According to the 2012 WHO classification, IMPC is defined as a subtype of IDC. There is no consensus established yet on the distinction between pure and mixed IMPC. Kaya et al.[15] and Wu et al.[18] considered 75% as a cutoff value. In our study, only tumors showing micropapillary growth patterns were considered pure, while other invasive types were considered as mixed IMPC.[13] In the study by Chen et al.[19], a higher incidence of LVI and LN metastasis

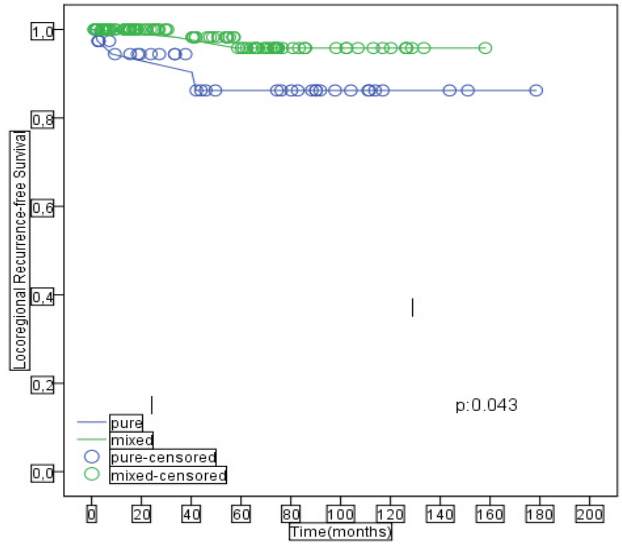

FIG. 2. Locoregional recurrence free survival curves of pure and mixed IMPC

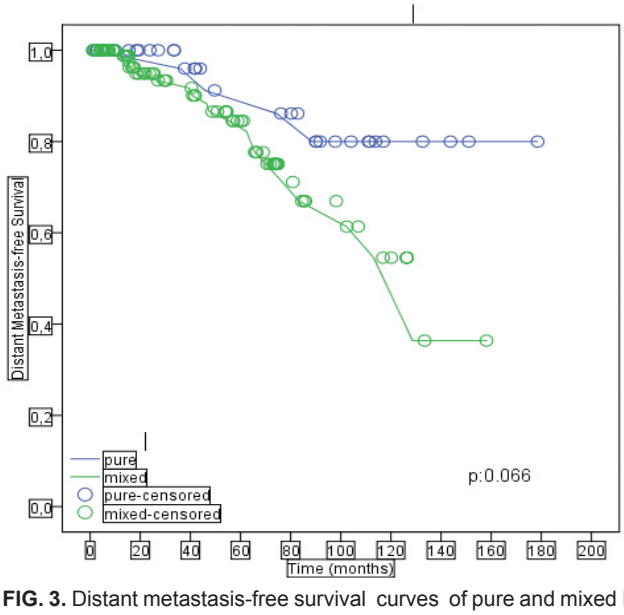

FIG. 3. Distant metastasis-free survival curves of pure and mixed IMPC cases

was noted in IMPC patients than in IDC patients, even in cases with < 25% of the IMPC component.[20] Other publications have reported that LN metastasis and survival rates were not related to the degree of micropapillary differentiation.[21,22]

In mixed cases, the type of breast cancer most associated with IMPC is IDC.[1,23] Likewise, in our study, IDC was recorded in 80 (78.4%) mixed IMPC cases, invasive lobular carcinoma in 8 cases (7.8%), and invasive mucinous carcinoma in 8 cases (7.8%). The most common component in mixed IMPC cases was IDC, as the only component in 71 cases (76.5%) and along with other components in 13 cases (12.7%).

Past studies have suggested that IMPC progresses with larger tumor size, higher LVI, LN metastasis, DM, and worse survival rates.[8,14] It has been shown that the rate of LN metastasis in IMPC is 46%-95%, and it is 34% in IDC 24,25. In our study, the frequency of LN metastasis in the entire group was 67%, which is consistent with the literature reports.

In a study comparing IMPC and IDC, Yu et al. found higher LVI and ECE positivity rates in IMPC patients. The 5-year LRRFS was lower in the IMPC group (79.1 vs. 93.3).[6] Chen et al.[19] demonstrated that the 5-year OS rate of IMPC was lower than that of IDC (59% vs. 77%). However, a few studies report no difference. In the study of Ho et al.[11], although there were more LVI and LN metastases in IMPC patients than in IDC, no significant difference was found in DFS and OS. Another study found longer OS in IMPC patients despite larger tumors, more positive LNs, and more advanced stages.[7] Chen and Ding[12] reported similar 5-year OS rates in a study comparing IMPC and triple-negative IDC patients (81.9%

TABLE 2. Survival Rates of Pure and Mixed IMPC Cases

	Pure IMPC (n: 39)	Mixed IMPC (n: 100)	p
	Survival rate (%)	Survival rate (%)	
5 year OS	90	91	0.839
5 year PFS	70	77	0.537
5 year LRRFS	86	95	0.043
5 year DMFS	88	83	0.066

OS, overall survival; PFS, progression-free survival; LRRFFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival

TABLE 3. Patterns of Failure of Pure and Mixed IMPC Cases

	Pure IMPC (n: 39)	Mixed IMPC (n: 100)	p
	Median (min - max) n (%)	Median (min - max) n (%)	
Progressive disease	7 (17.9)	20 (20)	0.784
Locoregional recurrence	4 (10.3)	2 (2)	0.052
Distant metastasis	4 (10.3)	19 (19)	0.213
Death with disease	3 (7.7)	6 (6)	0.716

min, minimum; max, maximum

TABLE 4. Studies Comparing Pure and Mixed IMPC Patients

Study	Number of cases	**LVI (*p*)**	**LN metastasis (*p*)**	**ER positivity (*p*)**	**PR positivity (*p*)**	**HER2 positivity (*p*)**
Gokce et al. [13], 2013	20 (pure IMPC) 83 (mixed IMPC)	94.1 94.8 (1.000)	78.9 79.7 (1.000)	57.9 73.2 (0.189)	61.1 81.4 (0.111)	46.7 53.8 (0.616)
Wang et al. [14], 2021	48 (pure IMPC) 73 (mixed IMPC)	68.8 58.9 (0.240)	81.3 75.4 (0.054)	75 76.7 (0.890)	41.7 52.1 (0.283)	31.2 32.9 (0.004)
Kaya et al. [15], 2018	19 (pure IMPC) 28 (mixed IMPC)	84.2 75 (0.449)	72.3 72.3 (NA)	89.5 60.7 (0.031)	78.9 60.7 (0.188)	28.6 78.9 (0.337)
Our study	45 (pure IMPC) 102 (mixed IMPC)	68.9 55.9 (0.138)	73.3 63.7 (0.255)	86.7 88.2 (0.789)	66.7 83.3 (0.024)	28.9 31.4 (0.763)

and 79.8%, respectively). Tang et al.[8] found the 5-year OS rate as 94.5% in the IMPC and 90.6% in the IDC. In our study, we found the 5-year OS rates of 90% and 91% for pure and mixed IMPC patients, respectively. The rate of OS varies widely in the literature, and our findings are consistent with the literature.

Chen et al. showed that different IMPC rates did not change the tumor size, histological grade, LN metastasis, and DM rates. However, metastatic LNs increased with increasing IMPC rate. When they compared IMPC patients and IDC patients, they found a higher LVI and LN metastasis rates in IMPC patients. They concluded that the presence of IMPC, even with a minor component, was associated with the aggressive nature of cancer.[19]

In previous studies, ER positivity rate has been reported as 25%-91%; PR positivity rate as 13%-82%; HER2 positivity rate as 36%100%; LVI rate as 33%-75%; and LN metastasis rate as 44%-100% in IMPC patients.[16,22,23,26-29] These data consisted of the results of studies involving all IMPC patients. However, only a few studies have provided separate results for pure and mixed subgroups.

HR, LVI, and LN metastasis positivity rates in studies comparing pure and mixed IMPC patients are summarized in Table 4.[13-15] In our study, 45 pure and 102 mixed IMPC patients were evaluated, and these numbers are higher than those in the literature. In addition, in our study, LVI and LN metastasis rates were lower, especially in the mixed group; this can be attributed to the higher ER (88.2%) and PR positivity (88.3%) rates in the mixed group than those reported in the literature. The PR positivity rate was higher in the mixed group than in the pure group (83.3% vs. 66.7%, *p*: 0.024).

Kaya et al. found the LVI and LN metastasis rates in the whole group were 78.7% and 72.3%, respectively.[15] Gokce et al.[13] found LVI and LN metastasis rates in the whole group as 94.7% and 79.6%, respectively. As seen in Table 4, these researchers found no difference between mixed IMPC and pure IMPC nor did they find any difference between low and high micropapillary ratios.

Wang et al.[14] reported a higher rate of LN metastasis in the pure IMPC group (81.3 vs. 75.4, *p*: 0.054). Although it was higher in the pure group, no statistically significant difference was noted in our study. They observed 10 deaths (7 with pure IMPC, 3 with mixed IMPC), with a mortality rate of 8.8%. The OS was significantly lower in the pure group.[14] In our study, the overall mortality rate was 6.5%. We detected 9 deaths (3 with pure IMPC and 6 with mixed IMPC). There was no difference in progressive disease, DM, and death with the disease rates. However, the LRR rates were different between the groups. Pure IMPC patients developed more LRRs (10.3% vs. 2%, *p*: 0.052). The 5-year LRRFS rate was already lower in the pure group (86% vs. 95%, *p*: 0.043). We believe that this might be elucidated by the comparatively high frequency of PR positivity in the mixed IMPC group (83.3% vs. 66.7%, *p*: 0.024). Yu et al.[6] found a 5-year LRRFS rate of 79.1% for the entire IMPC patient group and 93.1% for IDC patients. When compared with the literature, the LRRFS values were higher than IMPC patients and compatible with IDC patients.

The main limitation of this study is its retrospective and single-center nature. The same center did not evaluate the pathological specimens of the patients, and the degree of the micropapillary differentiation was not coded.

In conclusion, when compared with the literature, the number of patients in our study was greater than in studies comparing pure and mixed IMPC. The OS and LRRFS rates in our study were higher than in IMPC and compatible with IDC, which explains the higher ER and PR positivity rates. When we compared pure IMPC and mixed IMPC, we found that pure IMPC had a more aggressive nature. The PR positivity rate was lower in pure IMPC than in mixed IMPC, which may have attributed to this situation.

Ethics Committee Approval: Muğla Sıtkı Koçman University Medicine and Health Sciences Ethics Committee 210029/ 04.04.2022.

Data Sharing Statement: Data available on request from the authors. The data that support the findings of this study are available from the corresponding author.

Author Contributions: Concept- K.A.; Design- K.A.; Data Collection or Processing- G.E. ; Analysis or Interpretation- G.E.; Literature Search- G.E.; Writing- G.E.

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