Long-term Survival Outcomes of Invasive Micropapillary Carcinoma of the Breast: A Population-based Study

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Research article

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Abstract

Background: Whether or not invasive micropapillary carcinoma(IMPC) histology is an independent prognostic factor for breast cancer remains controversial. Moreover, the relationship between different molecular subtypes and survival outcomes of IMPC and invasive ductal carcinoma (IDC) is still unknown.

Methods: Using the SEER database to identify breast cancer patients, we retrospectively analyzed 959 IMPC and 174591 IDC cases diagnosed between 2010-2016 with non-metastatic diseases that underwent surgery. Specifically, we compared long-term outcomes of breast cancer-specific survival (BCSS) and overall survival (OS).

Results: Relative to IDC patients, IMPC patients were younger at diagnosis and had more moderate and poorly differentiated tumors (93.2% vs. 78.5%), more T3 and T4 tumors (11.0% vs. 6.9%), a higher percentage of nodal involvement (48.9% vs. 30.9%) and AJCC stage III patients (11.9% vs. 6.9%), and presented a higher proportion of HR positivity (91.2% vs. 82.3%) and HER2 positivity (22.3% vs. 16.9%). IMPC had a better BCSS (P=0.039) but showed no significant difference in OS (P=0.095) compared with IDC. In multivariate Cox analysis, IMPC histologic type was an independent favorable prognostic factor for both BCSS (HR=0.509, P=0.002, 95%CI: 0.335-0.775) and OS (HR=0.637, P=0.003, 95%CI: 0.475-0.854). After the case-control matched analysis using the propensity score matching method, IMPC still had a better BCSS (P=0.001); however, we observed no significant difference in OS (P =0.385). While different molecular subtypes have different impacts on survival outcomes, no significant differences were observed in BCSS and OS between IMPC and IDC in relation to Luminal B, HER2-enriched, and Triple-negative subtypes. However, in relation to the Luminal A subtype, IMPC had better BCSS (HR= 0.399, P=0.001, 95%CI: 0.226–0.703) and OS (HR=0.508, P=0.001, 95%CI: 0.345–0.746). In the case-control cohort, IMPC still had a better BCSS (HR= 0.423, P=0.005, 95%CI: 0.233–0.770), but no significantly difference was observed in OS (HR=0.767, P=0.22, 95%CI: 0.502–1.172) in Luminal A subtype.

Conclusion: Relative to IDC, IMPC presents better long-term survival outcomes, and the survival benefits are confined to the Luminal A subtype.

Introduction

Invasive micropapillary carcinoma (IMPC) is a relatively rare histologic subtype of invasive breast cancer, accounting for approximately 1.0–8.4% of all breast cancer cases[1–5].IMPC was first described in 1993, and classified as an independent breast tumor by the World Health Organization in 2003[6, 7].Pathologically, IMPC is known for a high incidence of lymphovascular invasion (LVI) and lymph node (LN) metastasis, and typically shows a more aggressive behavior than invasive ductal carcinomas (IDC).[1, 8–11]However, the utility of IMPC histology as an independent prognostic factor for breast cancer remains controversial. Several studies indicate that there is no significant difference in survival outcomes between IMPC and IDC patients when matched for lymph node status[1, 12].There is still controversy about the comparison of breast cancer-specific survival (BCSS) and overall survival(OS) between IMPC and

IDC[8, 9, 13]. Moreover, some studies have demonstrated similar BCSS and OS between IMPC and IDC. However, few previous studies have shown a detailed comparison based on breast cancer molecular subtype. This is likely because the breast cancer molecular subtypes have only been proposed in the past 20 years. Therefore, we conducted this study to compare the survival of IMPC and IDC in different molecular subtypes of breast cancer utilizing the Surveillance, Epidemiology, and End Results (SEER) database.

Materials And Methods

We retrospectively analyzed the SEER database released in 2019, including cases of primary breast cancer diagnosed between 2010-2016. Our inclusion criteria were female patients with histologically confirmed unilateral invasive ductal carcinoma (IDC) or invasive micropapillary carcinoma (IMPC), who were treated with surgery and without metastasis diseases at diagnosis. We excluded patients with more than one primary cancer or unknown data for a parameter of interest. The recorded patient characteristics included age at diagnosis, race, laterality, histologic grade, tumor size (T stage), lymph nodes positivity (N stage), staging (using AJCC 7th edition), hormonal receptor (HR) status, HER2 status, molecular subtype, and type of surgical procedure. Borderline estrogen receptor(ER) or progesterone receptor(PR) status was considered positive, and HR-positive was defined as ER and/or PR positive. Borderline HER2 status was defined as missing data. Comparisons of the characteristics between IDC and IMPC were performed using Pearson's Chi-square test. A univariate analysis using Kaplan-Meier survival curves was utilized to estimate BCSS and OS outcomes, and log-rank tests were performed to compare the two groups. Potential prognostic variables, including histologic subtype, age, race, laterality, grade, T stage, N stage, HR status, HER2 status, and surgery, were calculated using a Cox proportional hazard model for univariate and multivariate analyses. Subgroup analysis based on molecular subtype was performed to compare survival outcomes; for visualization purposes, the interaction effects of each molecular subtype on BCSS and OS were displayed using forest plots. To further diminish the effects of baseline difference between two groups, we applied the propensity score matching method. Specifically, each IMPC patient was matched to 3 IDC patients with similar characteristics, and survival outcomes of the matched groups were compared using the above methods repeatedly. Statistical analyses were performed using R statistical software (version 3.6.1, R Project for Statistical Computing, Vienna, Austria). A two-sided P value of<0.05 was considered statistically significant.

Results

Survival outcomes

For the total study population, the median follow-up was 39 months. A variety of potential prognostic variables were investigated for univariate and multivariate Cox analyses. Among these, age, race, tumor grade, T stage, N stage, HR status, and surgical type were found to be independent prognostic factors for both BCSS and OS. In multivariate Cox analysis, IMPC histologic type was an independent favorable prognostic factor for both BCSS (HR=0.509, P=0.002, 95%CI: 0.335-0.775) and OS (HR=0.637, P=0.003,

95%CI: 0.475-0.854) (Table 2 and 3). According to the comparisons between IMPC and IDC for the total population, IMPC displayed better BCSS (P=0.039), but showed no significant difference in OS (P=0.095) (Figure1).

A 1:3 matched case-control analysis was conducted to control for the effects of baseline differences between IMPC and IDC patients. A total of 959 IMPC patients were matched to 2877 IDC patients based on age, race, laterality, grade, T stage, N stage, HR status, HER2 status, molecular subtype, and surgery type. In each characteristic, no significant difference was observed between IMPC and the matched IDC cohort (Table 4). After the matched analysis, IMPC still had a better BCSS (P=0.001) but shown no significant difference in OS (P=0.385) compared with IDC (Figure 4).

In the subgroup analysis based on molecular subtype, different molecular subtypes were shown to have varying impacts on survival outcomes. For the total study population, no significant differences in BCSS and OS were observed between IMPC and IDC patients relative to Luminal B, HER2-enriched, and triple-negative subtypes. In comparing within the Luminal A subtype, IMPC had better BCSS (HR= 0.399, P=0.001, 95%CI: 0.226–0.703) and OS (HR=0.508, P=0.001, 95%CI: 0.345–0.746) (Figure 2 and 3). Additionally, for the case-control matched cohort, significant differences were not observed in both BCSS and OS between IMPC and IDC in Luminal B, HER2-enriched, and triple-negative subtypes. Within the Luminal A subtype, relative to IDC, IMPC patients were found to have better BCSS (HR= 0.423, P=0.005, 95%CI: 0.233–0.770), yet no significant difference was observed in OS (HR=0.767, P=0.22, 95%CI: 0.502–1.172) (Figure 5 and 6).

Discussion

IMPC is a rare type of breast cancer. Previous studies have shown that IMPC is more aggressive than IDC, with a worse prognosis. Moreover, IMPC typically has a high association for lymphovascular invasion (LVI) and lymph node (LN) metastasis. Many researchers consider IMPC a high-risk factor. However, previous studies have also suggested that IMPC has better long-term survival than IDC[14]. IMPC has favorable BCSS and OS rates[15]. Few studies have focused on the correlation between IMPC and survival due to a relatively low incidence. Moreover, there remains great controversy regarding this topic. Since the concept of breast cancer molecular subtype has been put forward in the past 20 years, most previous studies have not analyzed the survival based on molecular subtype. Therefore, we designed this study to analyze the relationship between survival of IMPC and IDC based on the molecular subtypes of breast cancer.

Using a Kaplan-Meier analysis to compare the survival of the two cancer types, we found differences in BCSS between the IMPC and IDC groups. However, we observed no effects on OS. This is consistent with the previous results of Chen et a[3, 4]l. Moreover, research from Yoon GY et al. was in agreement that the IMPC group showed a worse total recurrence-free survival(RFS) but found no significant difference in OS as well[20]. In their research, the IMPC group showed worse total RFS (hazard ratio [HR]=1.63, P=0.016), local RFS (HR=2.86, P=0.042), and distant RFS (HR=1.85 P=0.018), but there was no significant

difference in OS(HR=1.30, P=0.335). Other studies also suggested a lack of difference in BCSS and OS between the two groups in stage I breast cancer patients[14]. Hongliang Chen found that IMPC was correlated with aggressive clinical characteristics, such as larger tumors, more positive lymph nodes, and more advanced stage, relative to IDC. Additionally, a higher rate of ER/ PR positivity was observed in IMPC. These results are consistent with the research reported here. Further more, in a case-control analysis, the Hongliang Chen research still showed that IMPC was an independent favorable prognostic factor for BCSS (HR = 0.410, P < 0.001, 95% CI: 0.293-0.572) and OS (HR = 0.497, P < 0.001, 95% CI: 0.387-0.637). In subgroup analysis, IMPC routinely shows better survival outcomes compared with IDC, except for AJCC stage I and histologic grade I disease. However, data from Hao et al. suggested that there was a lack of difference in prognostic power between the two groups after the application of dependency matched analysis[21]. The survival analysis revealed no significant reduced overall survival (p = 0.752) or disease-free survival (p = 0.578) in IMPC patients. Moreover, multivariate Cox regression analysis revealed that IMPC was not an independent prognostic factor for disease-free survival (hazard ratio [HR] = 0.944; 95% confidential interval [CI], 0.601-1.481) or overall survival (HR = 0.727; 95% CI, 0.358-1.478). We further analyzed breast cancer molecular subtype dependent prognosis. We found that BCSS and OS were different between the IMPC and IDC group only in Luminal A subgroup, but not in Luminal B, triple-negative, and HER2-enriched subgroups. Lewis et al. also concluded that the prognosis of Triple-negative IMPC is as poor as that of IDC[22].

Considering the unbalanced data between the IMPC and IDC groups, propensity score matching (PSM) was used to adjust for potential baseline confounding between groups. After PSM, we still observe a difference in BCSS, but not OS, between the IMPC group and IDC group. Analysis by molecular subtype found that patients with Luminal A alone had differences in BCSS between the IMPC group and IDC group, yet no difference in OS. There is no difference in BCSS and OS between Luminal B, triple-negative, and HER2-enriched subtypes. Therefore, clinical characteristics consistency leads to a similar prognosis between the IMPC group and IDC, except for the Luminal A subtype. In our understanding, the Luminal A breast cancer subtype has a good prognosis, and most cases require only endocrine therapy without chemotherapy. In conclusion, the prognosis of IMPC of Luminal A is better than that of IDC.

Conclusion

In conclusion, IMPC is correlated with a favorable survival outcome compared with IDC. In addition, based on molecular subtype subgroup analysis, improved IMPC survival is limited to Luminal A. Therefore, in clinical practice, patients with the Luminal A subtype of IMPC may need less intensive treatment in comparison to IDC.

Abbreviations

BCSS, breast cancer-specific survival; OS, overall survival; IDC, invasive ductal carcinoma, IMPC, invasive micropapillary carcinoma; HR*, hormonal receptor; HER2, human epidermal growth receptor; PSM,

propensity score matching; PM, partial mastectomy; M, mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy.

Declarations

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Authors' contributions

XZ and FL conceived and drafted the study; XZ and FL conducted the literature research and collected all data; YS and QY analyzed and interpreted data; All authors commented on drafts of the paper and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not Applicable.

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Tables

Table 1 Patient characteristics

	IMPC (N=959)	(%)	IDC (N=174591)	(%)	P
Age					0.034
>60	480	50.1	81417	46.6	
≤60	479	49.9	93174	53.4	
Race					0.065
White	725	12.5	137399	78.7	
Black	120	11.9	18893	10.8	
Other	114	75.6	18299	10.5	
Laterality					0.556
Left	476	49.6	88324	50.6	
Right	483	50.4	86267	49.4	
Grade					<0.001
I	65	6.8	37592	21.5	
II	557	58.1	72483	41.5	
III or IV	337	35.1	64516	37.0	
Tumor size					<0.001
T1	541	56.4	109807	62.9	
T2	312	32.5	52875	30.3	
T3	80	8.3	7975	4.6	
T4	26	2.7	3934	2.3	
Lymph nodes					<0.001
N0	490	51.1	120566	69.1	
N1	288	30.0	40641	23.3	
N2	109	11.4	8922	5.1	
N3	72	7.5	4462	2.6	
Stage					<0.001
I	673	70.2	124350	71.2	
II	172	17.9	38155	21.9	

III	114	11.9	12086	6.9	
HR					<0.001
Negative	84	8.8	30861	17.7	
Positive	875	91.2	143730	82.3	
HER2					<0.001
Negative	745	77.7	145031	83.1	
Positive	214	22.3	29560	16.9	
Subtype					<0.001
Luminal A	705	73.5	123066	70.5	
Luminal B	170	17.7	20664	11.8	
HER2 enriched	44	4.6	8896	5.1	
Triple-negative	40	4.2	21965	12.6	
Surgery					<0.001
PM	561	58.5	106608	61.0	
M	201	21.0	41499	23.8	
MRM, RM or ERM	197	20.5	26484	15.2	

Abbreviations: IMPC, invasive micropapillary carcinoma; IDC, invasive ductal carcinoma; HR, hormonal receptor; HER2, human epidermal growth receptor 2; PM, partial mastectomy; M, mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy.

Table 2: Univariate and multivariate Cox proportional hazard model of breast cancer-specific survival (BCSS)

Variables	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Histology						
IDC	ref	ref				
IMPC	0.646	0.424-0.981	0.041	0.509	0.335-0.775	0.002
Age						
>60	ref	ref				
≤60	0.936	0.895-0.980	0.004	0.622	0.594-0.651	<0.001
Race						
Black	ref	ref				
White	0.504	0.476-0.534	<0.001	0.766	0.723-0.812	<0.001
Other	0.374	0.339-0.414	<0.001	0.545	0.492-0.603	<0.001
Laterality						
Left	ref	ref				
Right	0.957	0.914-1.001	0.06	0.961	0.918-1.006	0.085
Grade						
I	ref	ref				
II	3.817	3.330-4.375	<0.001	2.356	2.053-2.705	<0.001
III or IV	13.988	12.270-15.943	<0.001	4.978	4.343-5.707	<0.001
Tumor Size						
T1	ref	ref				
T2	4.541	4.287-4.810	<0.001	2.258	2.122-2.402	<0.001
T3	10.657	9.897-11.480	<0.001	3.696	3.403-4.015	<0.001
T4	19.775	18.279-21.390	<0.001	5.349	4.891-5.850	<0.001
Lymph nodes						
N0	ref	ref				
N1	3.158	2.988-3.338	<0.001	1.942	1.829-2.061	<0.001

N2	7.298	6.824-7.806	<0.001	3.345	3.102-3.606	<0.001
N3	13.688	12.756-14.688	<0.001	4.965	4.580-5.382	<0.001
HR						
Negative	ref	ref				
Positive	0.255	0.243-0.267	<0.001	0.461	0.438-0.484	<0.001
HER2						
Negative	ref	ref				
Positive	1.115	1.051-10182	<0.001	0.588	0.554-0.625	<0.001
Surgery						
M	ref			ref		
PM	0.594	0.560-0.632	<0.001	0.821	0.771-0.873	<0.001
MRM, RM or ERM	2.669	2.516-2.832	<0.001	1.106	1.038-1.178	0.002

Abbreviations: HR, hazard ratio; CI, confidence interval; IMPC, invasive micropapillary carcinoma; IDC, invasive ductal carcinoma; HR, hormonal receptor; HER2, human epidermal growth receptor 2; PM, partial mastectomy; M, mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy. 2. Multivariate analysis included histology, age, race, laterality, grade, tumor size, lymph nodes, HR status, HER2 status and surgery.

Table 3: Univariate and multivariate Cox proportional hazard model of overall survival (OS)

Variables	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Histology						
IDC	ref	ref				
IMPC	0.780	0.582-1.045	0.096	0.637	0.475-0.854	0.003
Age						
>60	ref	ref				
≤60	0.489	0.472-0.507	<0.001	0.372	0.359-0.384	<0.001
Race						
Black	ref	ref				
White	0.630	0.601-0.660	<0.001	0.790	0.753-0.828	<0.001
Other	0.406	0.374-0.441	<0.001	0.522	0.481-0.566	<0.001
Laterality						
Left	ref	ref				
Right	0.957	0.924-0.991	0.013	0.961	0.928-0.995	0.03
Grade						
I	ref	ref				
II	1.575	1.480-1.677	<0.001	1.204	1.130-1.284	<0.001
III or IV	3.397	3.203-3.603	<0.001	1.853	1.735-1.979	<0.001
Tumor Size						
T1	ref	ref				
T2	2.632	2.531-2.738	<0.001	1.911	1.830-1.996	<0.001
T3	4.905	4.623-5.204	<0.001	2.904	2.717-3.104	<0.001
T4	9.318	8.747-9.927	<0.001	4.194	3.901-4.510	<0.001
Lymph nodes						
N0	ref	ref				
N1	1.792	1.721-1.867	<0.001	1.314	1.257-1.375	<0.001

N2	3.568	3.376-3.770	<0.001	2.012	1.892-2.141	<0.001
N3	6.333	5.966-6.723	<0.001	2.975	2.779-3.186	<0.001
HR						
Negative	ref	ref				
Positive	0.403	0.388-0.418	<0.001	0.572	0.549-0.596	<0.001
HER2						
Negative	ref	ref				
Positive	0.976	0.931-1.023	0.303	0.660	0.629-0.693	<0.001
Surgery						
M	ref			ref		
PM	0.755	0.722-0.790	<0.001	0.847	0.809-0.887	<0.001
MRM, RM or ERM	2.171	2.070-2.277	<0.001	1.164	1.106-1.226	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; IMPC, invasive micropapillary carcinoma; IDC, invasive ductal carcinoma; HR, hormonal receptor; HER2, human epidermal growth receptor 2; PM, partial mastectomy; M, mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy. 2. Multivariate analysis included histology, age, race, laterality, grade, tumor size, lymph nodes, HR status, HER2 status and surgery.

Table 4 Matched patient characteristics

	IMPC	(N=959)	(%)	IDC	(N=2877)	(%)	P
Age							0.970
>60	480		50.1	1442		50.1	
≤60	479		49.9	1435		49.9	
Race							0.961
White	725		12.5	2188		76.1	
Black	120		11.9	353		12.3	
Other	114		75.6	336		11.7	
Laterality							0.911
Left	476		49.6	1422		49.4	
Right	483		50.4	1455		50.6	
Grade							0.849
I	65		6.8	180		6.3	
II	557		58.1	1682		58.5	
III or IV	337		35.1	1015		35.3	
Tumor size							0.992
T1	541		56.4	1622		56.4	
T2	312		32.5	946		32.9	
T3	80		8.3	232		8.1	
T4	26		2.7	77		2.7	
Lymph nodes							0.994
N0	490		51.1	1478		51.4	
N1	288		30.0	862		30.0	
N2	109		11.4	318		11.1	
N3	72		7.5	219		7.6	
Stage							0.623
I	673		70.2	2005		69.7	
II	172		17.9	497		17.3	

III	114	11.9	375	13.0	
HR					0.794
Negative	84	8.8	260	9.0	
Positive	875	91.2	2617	91.0	
HER2					0.875
Negative	745	77.7	2242	77.9	
Positive	214	22.3	635	22.1	
Subtype					0.985
Luminal A	705	73.5	2114	73.5	
Luminal B	170	17.7	503	17.5	
HER2 enriched	44	4.6	132	4.6	
Triple-negative	40	4.2	128	4.45	
Surgery					0.993
PM	561	58.5	1688	58.7	
M	201	21.0	598	20.8	
MRM, RM or ERM	197	20.5	591	20.5	

Abbreviations: IMPC, invasive micropapillary carcinoma; IDC, invasive ductal carcinoma; HR, hormonal receptor; HER2, human epidermal growth receptor 2; PM, partial mastectomy; M, mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy.

Figures

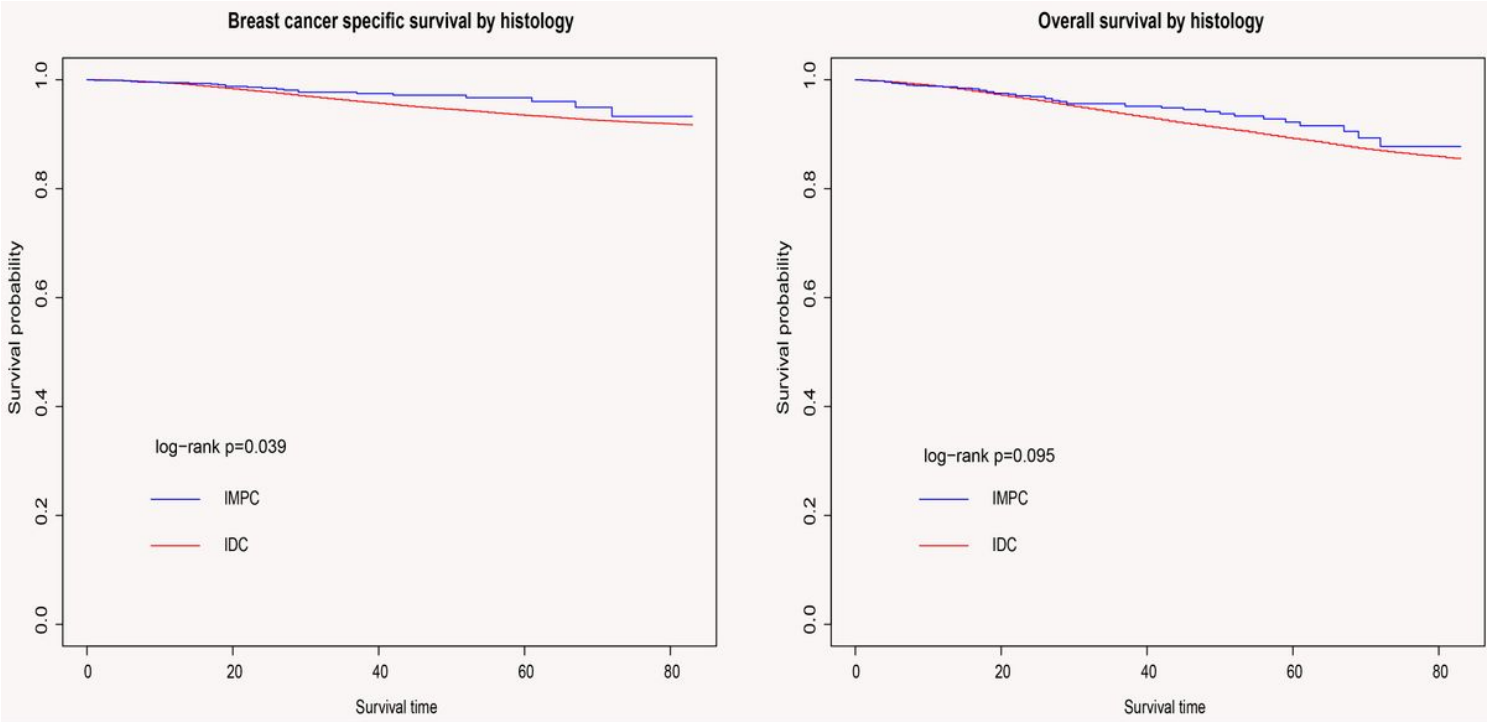

Figure 1

Kaplan-Meier curves of BCSS and OS based on the whole cohort, IDC vs. IMPC. Abbreviation: BCSS, breast cancer-specific survival; OS, overall survival; IDC, invasive ductal carcinoma, IMPC, invasive micropapillary carcinoma.

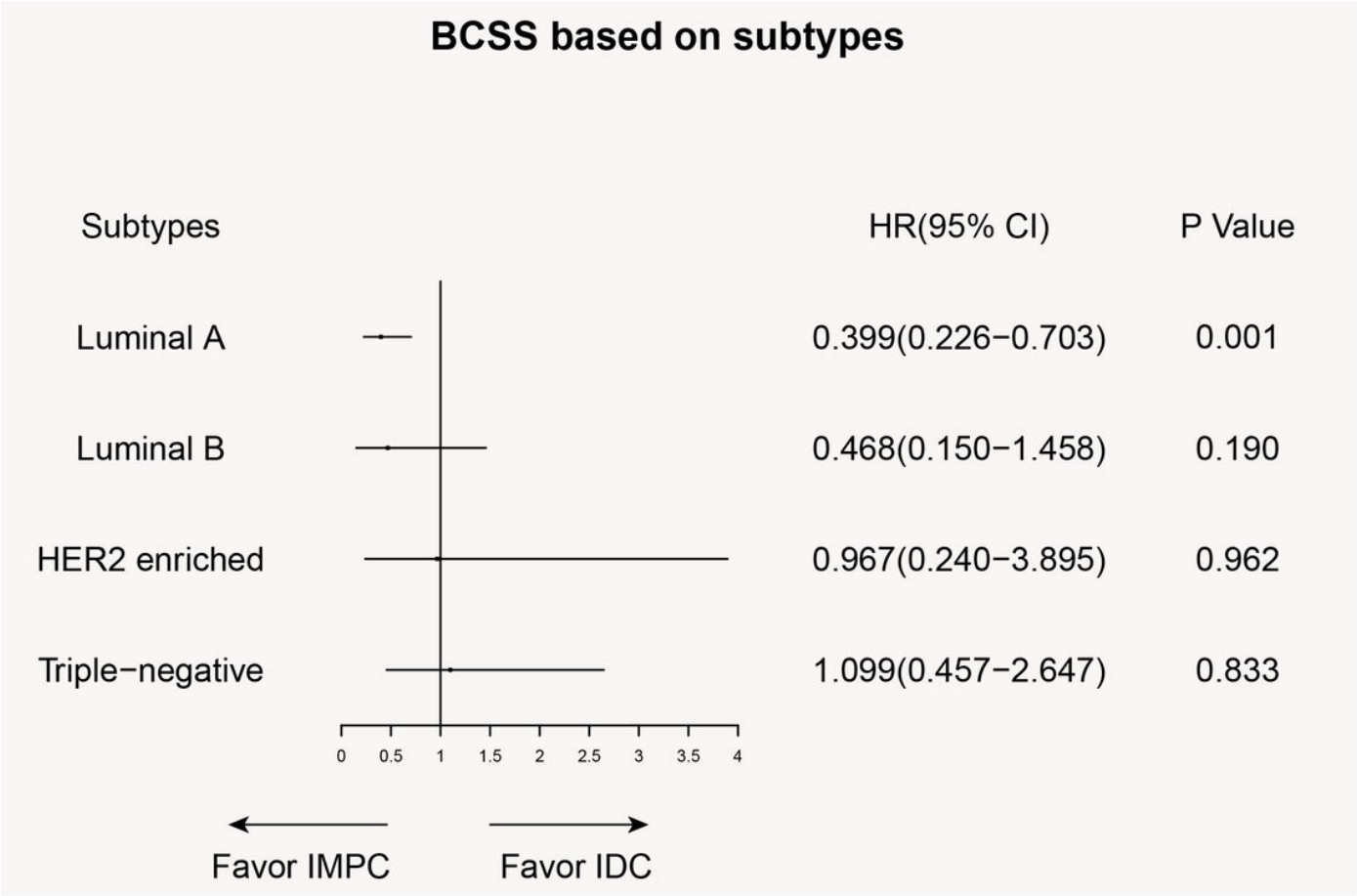

Figure 2

Forest plot of BCSS based on molecular subtypes. The hazard ratio(HR) was calculated by multivariate Cox proportional hazard model, and the covariates included histology, age, race, laterality, grade, tumor size, lymph nodes, HR* status, HER2 status and surgery. The data source was the whole cohort. Abbreviation: BCSS, breast cancer-specific survival; HR*, hormonal receptor; HER2, human epidermal growth receptor.

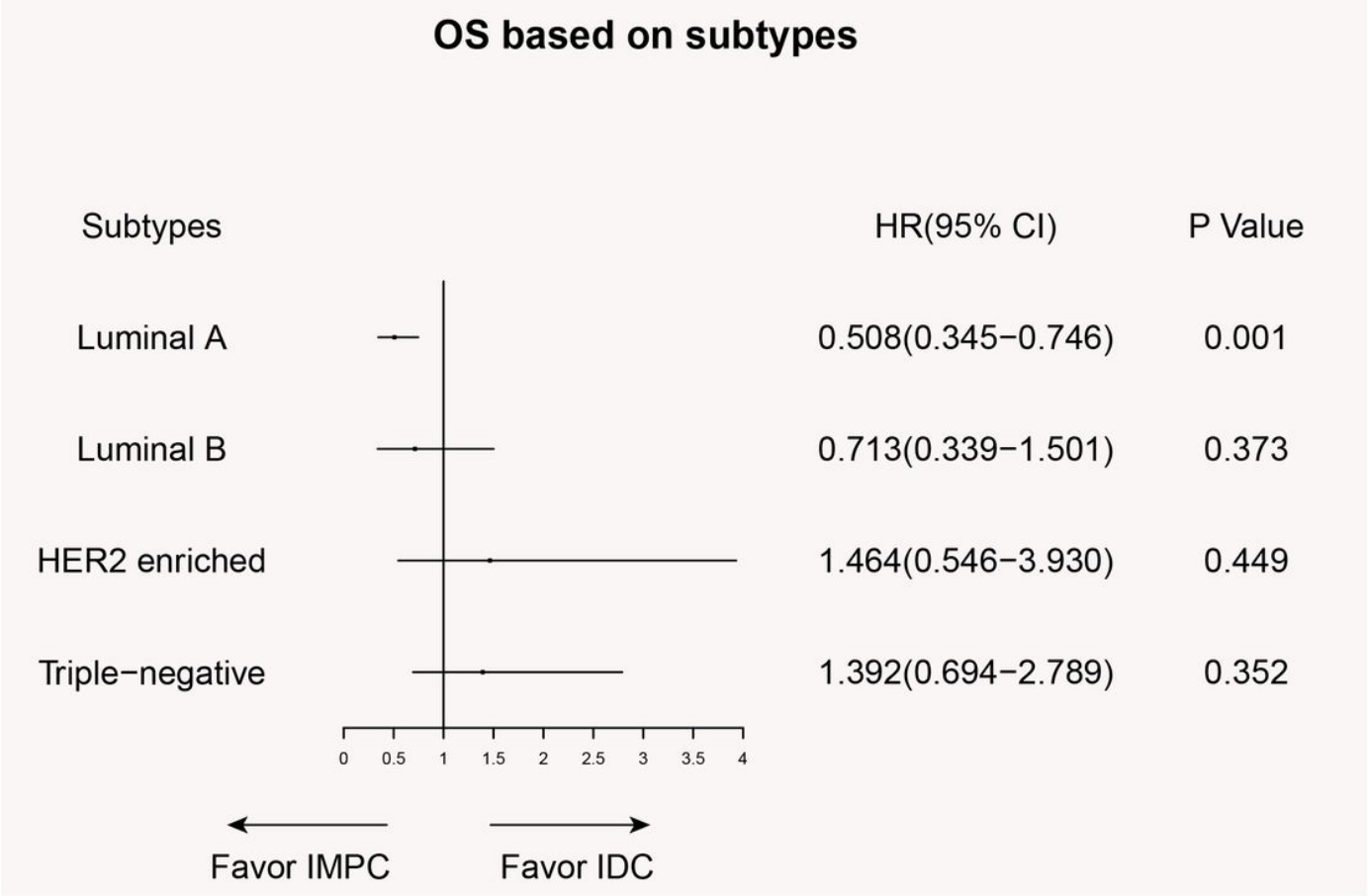

Figure 3

Forest plot of OS based on molecular subtypes. The hazard ratio(HR) was calculated by multivariate Cox proportional hazard model, and the covariates included histology, age, race, laterality, grade, tumor size, lymph nodes, HR* status, HER2 status and surgery. The data source was the whole cohort. Abbreviation: OS, overall survival; HR*, hormonal receptor; HER2, human epidermal growth receptor.

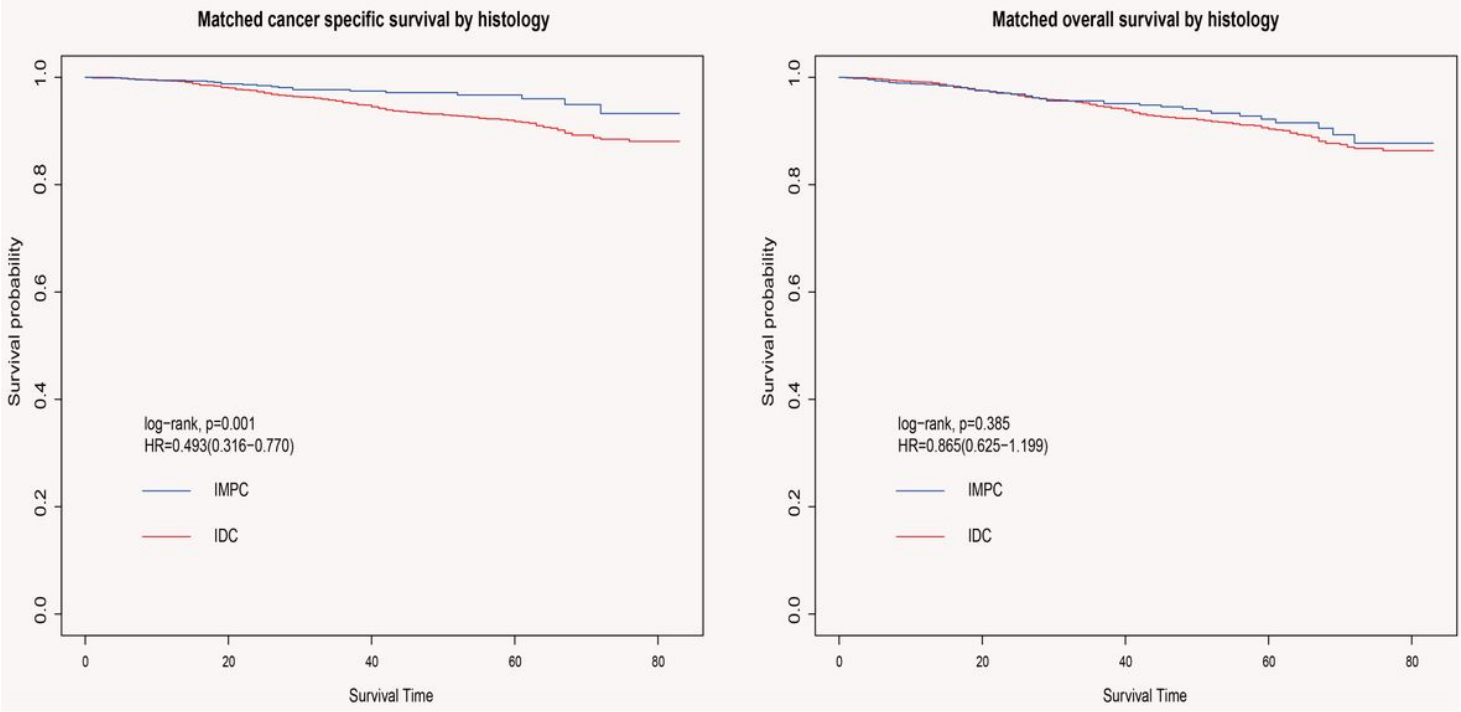

Figure 4

Kaplan-Meier curves of BCSS and OS based on the matched cohort, IDC vs. IMPC. Abbreviation: BCSS, breast cancer-specific survival; OS, overall survival; IDC, invasive ductal carcinoma, IMPC, invasive micropapillary carcinoma.

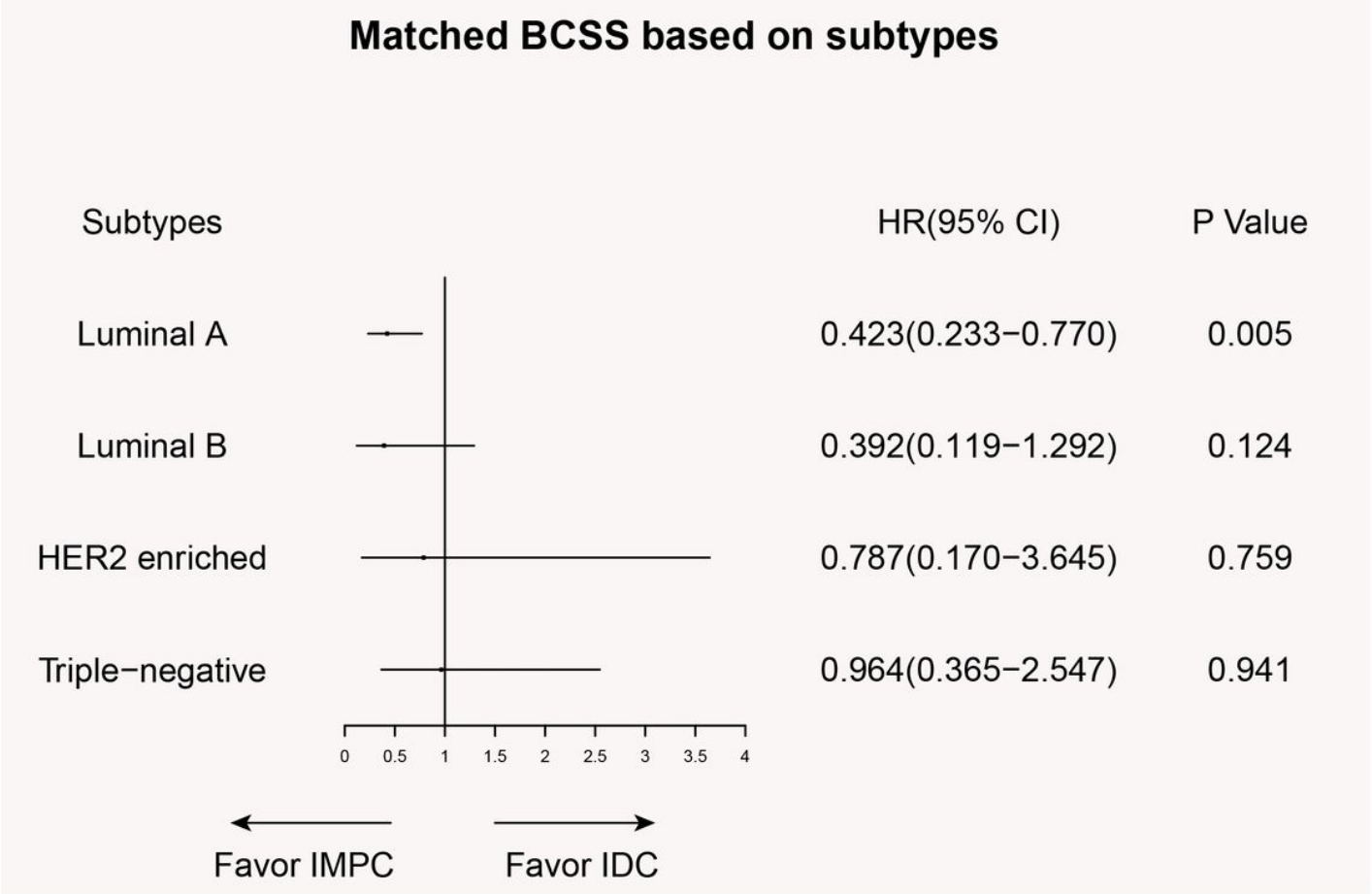

Figure 5

Forest plot of BCSS based on molecular subtypes. The hazard ratio(HR) was calculated by univariate Cox proportional hazard model. The data source was the matched cohort. Abbreviation: BCSS, breast cancer-specific survival.

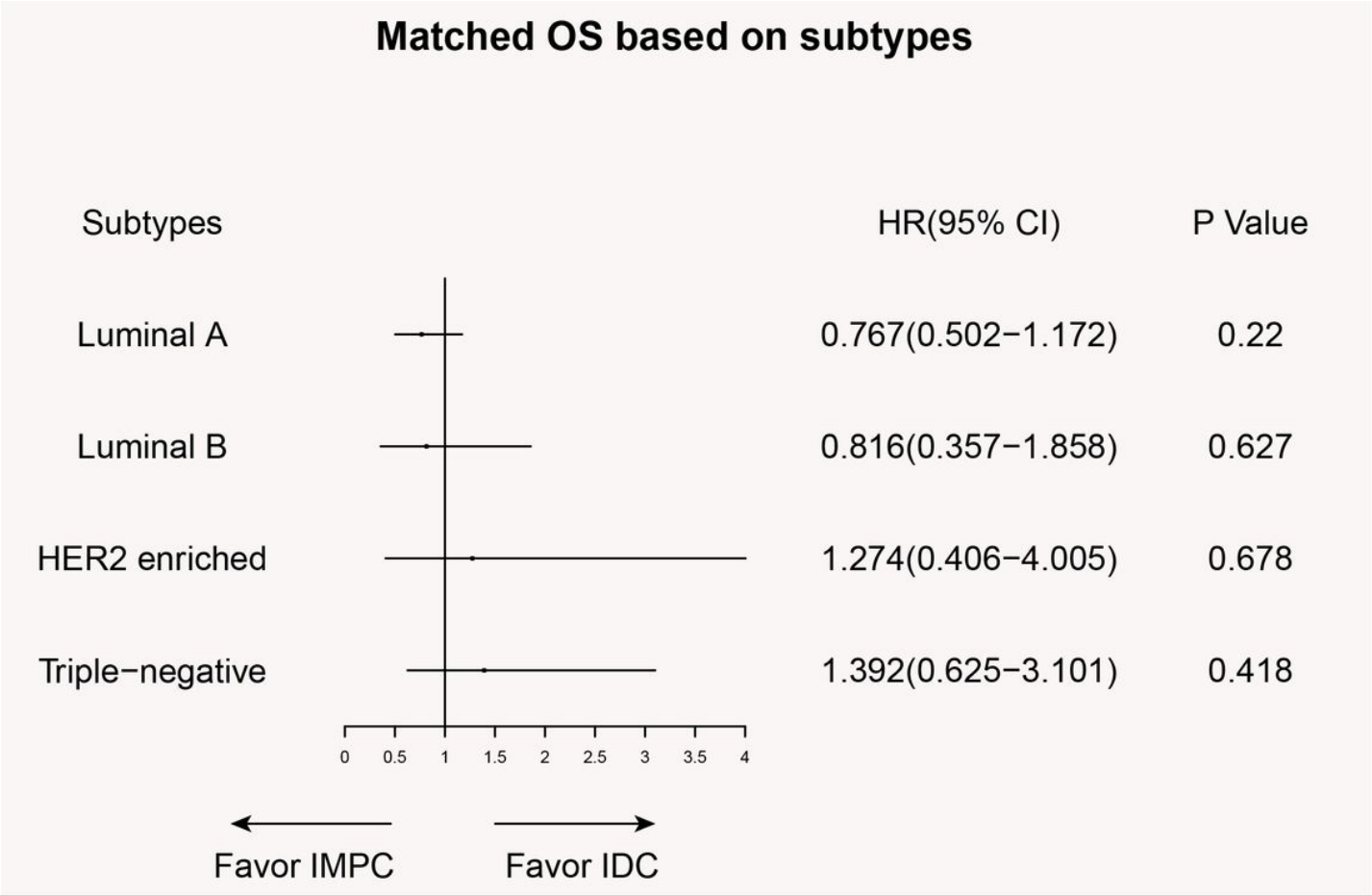

Figure 6

Forest plot of OS based on molecular subtypes. The hazard ratio(HR) was calculated by univariate Cox proportional hazard model. The data source was the matched cohort. Abbreviation: OS, overall survival.