An analysis of invasive micropapillary breast carcinoma based on hormone receptor and epidermal growth receptor 2 status

Yuting Sun (✉ 21718312@zju.edu.cn)
Zhejiang University

Research article

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Abstract

Background

This research aimed to explore the role of combining hormone receptor (HR) with epidermal growth factor receptor 2 (Her-2) status of invasive micropapillary breast carcinoma (IMPC).

Methods

1291 IMPC patients were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute. The χ^2 test and Fisher's exact probability test were used to evaluate differences between qualitative variables. Univariate and multivariate Cox proportional hazards regressions were performed to assess the independent prognostic factors on cancer-specific survival (CSS) and overall survival (OS). The nomogram models were made to predict 3-year survival rate of IMPC using R software.

Results

Among 1291 patients, HR+/Her-2- subtype accounted for 74.7%, while HR-/Her-2+, HR-/Her-2-, HR+/Her-2 + accounted for 4.7%, 4.0% and 15.6% respectively. The χ^2 test indicated compared to HR+/Her-2- subgroup, HR-/Her-2- or HR+/Her-2 + subtype IMPC had larger tumor size (T stage) and higher histological grade. Compared to HR+/Her-2- IMPC, HR-/Her-2- and HR+/Her-2 + subtypes were more likely to receive mastectomy than conserving surgery. Furthermore, HR+/Her-2- IMPC had more projections to receive chemotherapy and was less likely to receive radiotherapy compared with HR-/Her-2- subtype. Survival analysis suggested that HR-/Her-2- IMPC had the worst OS and CSS.

Conclusion

This population-based study provided evidence that HR-/Her-2- IMPC accounted the smallest part of four subtypes, but were more likely to have larger tumor size and more advanced histological grade. Furthermore, HR+/Her-2- IMPC had most unfavorable prognosis among four subtypes.

Background

IMPC was a rare special type of breast cancer,¹ composed of small, hollow or morula-like clusters of cancer cells, surrounded by clear stromal spaces.² Several studies have illuminated that IMPC had higher rates of positive axillary lymph nodes, larger tumor size, more advanced histological grade than IDC.^{3 4 5 6} Despite its highly aggressive clinical performance, a study found that IMPC had a better long-term survival outcome comparing with IDC.⁵ A meta-analysis found that IMPC patients were more likely to have local regional recurrence(LRR) than IDC, but the OS and CSS were not significantly different between IMPC and IDC.⁷ A population based study showed that hormone positive IMPC had a better survival.⁸ And prior studies have compared prognosis based on HR or Her-2 status between IMPC and IDC.⁹ However, they did not combine these two factors together to analyze its impact on survival of IMPC. Here, in this study, we divided IMPC into four molecular subtypes according to hormone receptor (including estrogen receptor (ER) and progesterone receptor (PR)) and epidermal growth factor receptor 2(Her-2) status to analyze the features of IMPC in a more reasonable way.

Methods

Data collection

The SEER*Stat (version 8.3.5) Case Listing session was used to get 1291 cases of IMPC (8507/3: Ductal carcinoma, micropapillary). In consideration of the information on breast cancer molecular subtype was not available until 2010, we selected IMPC patients from 2010 to 2015 from the Surveillance, Epidemiology, and End Results(SEER), version 8.3.5. The deadline for follow-up time was November 2016. The morphological classification of breast cancer was Ductal carcinoma, micropapillary according to Oncology, version 3(ICD-O-3). All patients included in this study were female, and patients with unknown subtype, ethnicity, T stage, N stage, M stage and grade were excluded from this study.

Clinicopathological factors

In this study, we used the 7th AJCC version to evaluate TNM (T: tumor size; N: axillary lymph nodes metastasis; M: distant metastasis) and stage. IMPC was classified into four molecular types according to the expression of hormone receptor(HR) and epidermal growth factor receptor 2 (HER2): HR+/Her-2-, HR-/Her-2+, HR-/HER2-, HR+/HER2+. According the criterion of SEER database, the definition of hormone receptor positive was as follows: either ER positive or PR positive, and if 1% or greater cells stained positive, the test results of ER or PR was considered positive. HER2 expression was examined by any of following ways in laboratories: fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) or chromogenic in situ hybridization (CISH). Her-2 positive meant it was amplified or overexpression in any of these three ways. Surgery type was sorted into three types: mastectomy, breast-conserving surgery, and no surgery or not recommended. And we got the permission to obtain chemotherapy and radiotherapy data of patients from the SEER.

Statistical analysis

SPSS Statistics software (version 23.0) was used to analyze the data. X^2 test was used to analyze the characteristics of IMPC. The Kaplan-Meier method was used to construct the OS and CSS of IMPC. The Cox proportional hazards regression model was used to determine the independent prognostic factors for OS and CSS. Hazard ratios (HRs) with corresponding 95% CI were used to show the effect of factors on OS and CSS. A p value of < 0.05 was considered statistically significant. To present the prognostic factors of IMPC more clearly, we use nomogram models to show factors that have impacts on OS and CSS of IMPC.

Results

In this study, we made comparisons in four groups using X^2 test: HR+/Her-2- vs. HR-/Her-2-, HR+/Her2- vs. HR+/Her-2+, HR-/Her-2 + vs. HR-/Her-2-, HR-/Her-2 + vs. HR+/Her-2+. The characteristics of four subtypes of IMPC were shown in Table 1. There were 964 (74.7%) IMPC patients belonging to HR+/Her-2- subtype, which accounted for the largest number of population in this study. HR-/Her-2- subtype was the smallest part which accounted for only 4.0%. Most patients were over 50 years old when they were diagnosed with IMPC (80.0%). 614 of 1291 (47.6%) IMPC patients had positive axillary lymph nodes when first diagnosis which suggested IMPC had a high ratio of lymph node invasion. A mastectomy was performed in 590 (45.7%) patients and 642 (49.7%) patients received conserving surgery.

Table 1
Characteristics of four subtypes of IMPC patients

variables	HR+/ Her-2-(%)	HR-/ Her-2+ (%)	HR-/ Her-2- (%)	HR+/ Her-2+(%)	N(%)	p^1	p^2	p^3	p^4
Ages									
< 50	166(17.2)	14(23.0)	12(23.1)	66(30.8)	258(20.0)	0.297	0.000	0.987	0.231
>=50	798(82.64)	47(77.0)	40(76.9)	148(69.2)	1033(80.0)				
Ethnicity									
black	116(12.0)	10(19.2)	10(19.2)	28(35.9)	161(12.5)	0.300	0.109	0.508	0.433
white	738(76.6)	36(69.2)	36(69.2)	172(46.2)	993(76.9)				
others	110(11.4)	6(11.5)	6(11.5)	14(17.9)	137(10.6)				
T stage									
T1	571(59.2)	33(54.2)	19(36.5)	107(57.0)	730(56.6)	0.004	0.024	0.109	0.402
T2-3	359(37.2)	22(36.1)	29(55.8)	94(43.9)	504(39.0)				
T4	34(3.5)	6(9.8)	4(7.7)	13(6.1)	57(4.4)				
N stage									
N0	524(54.4)	30(49.2)	22(42.3)	101(47.2)	677(52.4)	0.175	0.150	0.743	0.753
N1-2	373(38.7)	24(39.3)	24(46.2)	94(43.9)	515(39.9)				
N3	67(7.0)	7(11.5)	6(11.5)	19(8.9)	99(7.7)				
M stage									
M0	936(97.1)	55(90.2)	48(92.3)	204(95.3)	1243(96.3)	0.054	0.185	0.751	0.129
M1	28(2.9)	6(9.8)	4(7.7)	10(4.7)	48(3.7)				
Grade									
G 1–2	677(70.2)	29(47.5)	15(28.8)	111(51.9)	832(64.4)	0.000	0.000	0.042	0.551
G 3–4	287(29.8)	32(52.5)	37(71.2)	103(48.1)	459(35.6)				
Stage									
stage I	435(45.1)	27(44.3)	16(30.8)	83(38.8)	561(43.5)	0.080	0.000	0.357	0.252
stage II	334(34.6)	16(26.2)	21(40.4)	59(27.6)	430(33.3)				
stage III	167(17.3)	12(19.7)	11(21.2)	62(29.0)	252(19.5)				
stage IV	28(2.9)	6(9.8)	4(7.7)	10(4.7)	48(3.7)				
Surgery type									

p^1 : HR+/Her-2- vs. HR-/Her-2-; p^2 : HR+/Her2- vs. HR+/Her-2+;

p^3 : HR-/Her-2 + vs. HR-/Her-2-; p^4 : HR-/Her-2 + vs. HR+/Her-2+

variables	HR+/ Her-2-(%)	HR-/ Her-2+ (%)	HR-/ Her-2- (%)	HR+/ Her-2+ (%)	N(%)	p^1	p^2	p^3	p^4
no/unknown	38(3.9)	4(6.6)	3(5.8)	14(6.5)	59(4.6)	0.065	0.006	0.985	0.730
mastectomy	414(42.9)	35(57.4)	30(54.5)	111(51.9)	590(45.7)				
conserving surgery	512(53.1)	22(36.1)	19(40.0)	89(41.6)	642(49.7)				
Radiotherapy									
no/unknown	545(56.5)	32(52.5)	23(44.3)	99(46.3)	699(54.1)	0.082	0.006	0.383	0.393
yes	419(43.5)	29(47.5)	29(55.8)	115(53.7)	592(45.9)				
Chemotherapy									
no/unknown	389(40.4)	53(86.9)	34(65.4)	166(77.6)	642(49.7)	0.000	0.000	0.007	0.111
yes	575(59.6)	8(13.1)	18(34.6)	48(22.4)	649(50.3)				
p ¹ : HR+/Her-2- vs. HR-/Her-2-; p ² : HR+/Her2- vs. HR+/Her-2+;									
p ³ : HR-/Her-2 + vs. HR-/Her-2-; p ⁴ : HR-/Her-2 + vs. HR+/Her-2+									

Clinical Pathological features

Comparing with HR-/Her-2- subgroups, HR+/Her-2- and HR-/Her-2 + IMPC patients had a higher proportion of Grade I (well differentiated) or Grade II (moderately differentiated) (HR-/Her2- vs. HR+/Her-2-, $p < 0.001$; HR-/Her-2- vs. HR+/Her-2+, $p = 0.042$). Patients with HR+/Her-2- features were more likely to receive chemotherapy while HR-/Her-2 + groups had less proportions of receiving chemotherapy compared with HR-/Her-2- group (HR+/Her2- vs. HR-/Her-2-, $p < 0.001$; HR-/Her-2 + vs. HR-/Her-2+, $p < 0.001$). Furthermore, comparing to HR+/Her-2- IMPC patients, patients with HR+/Her-2 + status had larger tumor size ($p = 0.024$), worse histological grade ($p < 0.001$) and were less likely to accept chemotherapy ($p < 0.001$) and surgery treatments ($p = 0.006$).

In addition, we made further analysis of the two surgery types (data showed in Table 2), and we found that comparing with HR+/Her-2- subtype, HR+/Her-2 + and HR-/Her-2- IMPC patients were more likely to receive mastectomy than conserving surgery.

Table 2
Comparison of two surgery types based on four subtypes of IMPC

Surgery type	HR+/ Her-2-(%)	HR-/ Her-2+ (%)	HR-/ Her-2- (%)	HR+/ Her-2+ (%)	N(%)	p^1	p^2	p^3	p^4
Mastectomy	414(44.7)	35(61.4)	30(61.2)	111(55.5)	590(47.9)	0.024	0.006	0.985	0.427
Conserving surgery	512(55.3)	22(38.6)	19(38.8)	89(44.5)	642(52.1)				
p ¹ : HR+/Her-2- vs. HR-/Her-2-; p ² : HR+/Her2- vs. HR+/Her-2+;									
p ³ : HR-/Her-2 + vs. HR-/Her-2-; p ⁴ : HR-/Her-2 + vs. HR+/Her-2+									

Potential prognostic factors of OS and CSS

The 3-year OS of HR+/Her-2-, HR-/Her-2+, HR-/Her-2- and HR+/Her-2 + were 93.2%, 97.9%, 70.9% and 88.3 respectively. On univariate analysis, ethnicity, subtype, histological grade, tumor size, distant metastasis, surgery type, chemotherapy and radiotherapy were found to be prognostic factors for OS of IMPC. For CSS, the prognostic factors were ethnicity, subtype, histological grade, T stage, N stage, M stage, surgery type and radiotherapy. Univariate analysis data was shown in Table 3. We also conducted two nomogram models to predict prognostic factors of invasive micropapillary breast carcinoma's 3-year survival rate (OS, Fig. 1, supplementary Fig. 1; CSS: Fig. 2, supplementary Fig. 2). The nomogram plot showed the calibration was ideal.

Table 3
univariate analysis for IMPC patients

variables	OS		CSS	
	HR (CI 95%)	P value	HR (CI 95%)	p value
Age				
< 50	1	-	1	-
>=50	1.578(0.811–3.072)	0.179	1.226(0.510–2.947)	0.648
Ethnicity				
black	1	-	1	-
white	0.560(0.321–0.977)	0.041	0.372(0.177–0.783)	0.009
other	0.297(0.099–0.890)	0.030	0.350(0.096–1.273)	0.111
Grade				
G 1–2	1	-	1	-
G 3–4	1.700(1.081–2.675)	0.022	2.599(1.339–5.042)	0.005
T stage				
T1	1	-	1	-
T2-3	1.460(0.887–2.402)	0.136	2.750(1.226–6.170)	0.014
T4	7.421(3.868–14.238)	0.000	19.917(7.687–47.048)	0.000
N stage				
N0	1	-	1	-
N1-2	1.414(0.869–2.301)	0.163	2.836(1.291–6.228)	0.009
N3	1.869(0.916–3.815)	0.086	4.349(1.618–11.691)	0.004
M stage				
M0	1	-	1	-
M1	10.216(5.846–17.864)	0.000	18.807(9.318–37.961)	0.000
Subtype				
HR+/Her-2-	1	-	1	-
HR-/Her-2+	0.618(0.150–2.544)	0.505	0.611(0.083–4.519)	0.629
HR-/Her-2-	5.110(2.651–9.850)	0.000	5.896(2.407–14.443)	0.000
HR+/Her-2+	1.481(0.816–2.687)	0.197	1.087(0.414–2.850)	0.866
Surgery type				
no surgery	1	-	1	-
mastectomy	0.109(0.061–0.196)	0.000	0.122(0.056–0.266)	0.000
CI = 95% confidence interval; HR = hazard ratio				

variables	OS		CSS	
Conserving sugary	0.087(0.048–0.157)	0.000	0.049(0.019–0.125)	0.000
Chemotherapy				
no/unknown	1	-	1	-
yes	1.908(1.195–3.048)	0.007	1.172(0.609–2.253)	0.635
Radiotherapy				
yes	1	-	1	-
no/unknown	4.712(2.744–8.094)	0.000	2.851(1.425–5.703)	0.003
CI = 95% confidence interval; HR = hazard ratio				

Multivariate variate analysis revealed that histological grade, tumor size, distant metastasis, subtype, surgery type, and radiotherapy were prognostic factors for OS and CSS. Though it has been determined IMPC's aggressive behavior related to its high proportions of axillary lymph node metastases, nodal stage was not a prognostic factor on OS and CSS in this study. Multivariate analysis data was shown in Table 4.

Table 4
multivariate analysis for IMPC patients

Variables	OS		CSS	
	HR(95%CI)	p value	HR(95%CI)	p value
Ethnicity				
black	1	-	1	-
white	0.702(0.393–1.254)	0.231	0.508(0.232–1.113)	0.090
others	0.375(0.124–1.135)	0.083	0.512(0.136–1.926)	0.322
Grade				
G 1–2	1	-	1	-
G 3–4	1.844(1.160–2.932)	0.010	2.050(1.046–4.020)	0.037
T stage				
T1	1	-	1	-
T2-3	1.723(1.025–2.895)	0.040	2.358(1.039–5.351)	0.040
T4	4.840(2.032–11.528)	0.000	5.682(1.862–17.339)	0.002
N stage				
N0	-	-	1	-
N1-2	-	-	1.560(0.648–3.759)	0.321
N3	-	-	1.287(0.400-4.143)	0.673
M stage				
M0	1	-	1	-
M1	2.743(1.240–6.066)	0.013	7.519(3.083–18.337)	0.000
Subtype				
HR+/Her-2-	1	-	1	-
HR-/Her-2+	1.173(0.274–5.020)	0.830	0.509(0.067–3.883)	0.515
HR-/Her-2-	7.625(3.720–15.630)	0.000	5.511(1.770-15.936)	0.003
HR+/Her-2+	2.172(1.168–4.086)	0.015	0.961(0.347–2.657)	0.938
Surgery type				
no surgery	1	-	1	-
mastectomy	0.298(0.143–0.621)	0.001	0.453(0.163–1.261)	0.130
Conserving surgery	0.482(0.210–1.107)	0.085	0.410(0.109–1.548)	0.188
Chemotherapy				
yes	1	-	-	-
CI = 95% confidence interval; HR = hazard ratio				

Variables	OS		CSS	
no/unknown	2.540 (1.508–4.279)	0.000	-	-
Radiotherapy			-	-
yes	1	-	1	-
no/unknown	4.312(2.369–7.851)	0.000	3.234(1.601–6.531)	0.001
CI = 95% confidence interval; HR = hazard ratio				

HR-/Her-2- subtype IMPC had the worst prognosis

Among the four subtypes, HR-/Her-2- subtype IMPC had the worst OS ($p < 0.001$) and CSS ($p < 0.001$) (Fig. 3, 4).

Discussion

Breast cancer could be divided into four subtypes according to hormone status, epidermal growth factor 2 status and Ki-67 expression level. In recent years, it has been widely accepted that treatments for breast cancer should be based on different molecular subtypes. Most studies' explorations were based on nonspecific breast cancer. But IMPC was a special and rare type of breast cancer, which behaved more aggressively than invasive ductal breast carcinoma. Previous clinical studies proved that breast cancer with ER and PR positive status was associated with better OS and CSS.^{5 10 11} Several studies suggested that molecular subtype of breast cancer provided additional prognostic information regarding patient outcomes.^{12 11 13} A population based study showed that hormone positive IMPC had a better survival.⁸ Therefore, in this study we used breast cancer molecular type to analyze the impact of combination HR with Her-2 status on IMPC. Our results indicated that HR-/Her-2- subtype had the most unfavorable prognosis.

As was mentioned above, hormone positive status was associated with better OS and CSS, many studies separately analyzed the effects of hormone receptor and HER2 expression status on IMPC.^{9 8} In fact, many previous research has proven that molecular subtype can affect prognosis on breast carcinoma.^{12 14 15} Here in this study, multivariate analysis indicated that only HR-/Her-2- subtype had a worse prognosis on OS and CSS comparing to HR+/HER2- subtype, suggesting that Her-2 expression status might play an important role, especially when both hormone receptor and Her-2 were negative.

Comparing with other three subtypes, HR-/Her-2- IMPC had more aggressive behaviors, for it had larger tumor size and more advanced histological grade and stage. Tumors which performed more aggressively were more possible to receive surgery, chemotherapy and radiotherapy. And further analysis showed that HR-/Her-2- and HR+/Her-2 + subtype had more proportions to receive mastectomy than HR+/Her-2- subtype, this was might because that HR+/Her-2- status IMPC had better biological behaviors.

We conducted a nomogram models to predict 3-year survival rate of IMPC. This tool allowed us to estimate patients' survival according to individual characteristics. For instance, a HR-/Her-2- IMPC patient who was at 50-year-old, black ethnicity, T4N3M1 stage, receiving surgery and adjuvant therapy, the 3-year overall survival rate was only 50% while at the same condition, 3-year overall survival rate of HR+/Her-2- subtype could reach to about 92%. From this model, we could find that at the same background, chemotherapy and radiotherapy had smaller influence on CSS than on OS. This model made it more clear for clinical doctors to assess survival rate of IMPC patients, particularly evaluating survival rate of different subtype IMPC, thus to help doctors to make more accurate and valuable treatments strategies.

However, this study did not obtain data on specific chemotherapy regimens which might affect prognosis. And we could not obtain data about whether Her-2 positive patients received targeted therapy (Herceptin) or not. Because the patients with Her-2 expression information only started from 2010, we selected breast cancer patients from 2010 to 2015, which might lead to insufficient follow-up time. It is necessary to follow up longer time to verify our findings. When typing breast cancer, the factor of Ki-67 is lacking, a factor that is practical for most breast cancers. And it would be better to acquire data about local recurrence rate (LRR), recurrence-free interinterval (RFI) and distant relapse-free survival (DRFS) data to make a more complete analysis of the four subtypes of IMPC.

Conclusion

This population-based study provided evidence that HR-/Her-2- IMPC accounted the smallest part of four subtypes, but were more likely to have larger tumor size and more advanced histological grade. Furthermore, HR+/Her-2- IMPC had most unfavorable prognosis among four subtypes.

Abbreviations

IMPC: invasive micropapillary carcinoma; IDC: invasive ductal carcinoma; OS: overall survival; CSS: cancer-specific survival; HR: hormone receptor; ER: estrogen receptor; HER2: human epidermal growth receptor 2.

Declarations

Ethics approval and consent to participate:

not applicable

Consent for publication:

The only author Yuting Sun agree to submit this manuscript.

Competing Interests:

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Yuting Sun did all work to this job.

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Data statement: The data support the findings of this study are available from the SEER database but restriction apply to the availability of these data, which were used under license for current study, and so are not publicly available.

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Figures

Figure 1

3-year overall survival nomogram models of IMPC patients.

Figure 2

3-year overall survival nomogram models of IMPC patients.

Overall survival of four subtypes

Figure 3

Overall survival of four subtypes IMPC patients. Log-rank test was used to verify p value, and $p < 0.05$ means statistically significant.

Cancer-specific survival of four subtypes

Figure 4

cancer-specific survival of four subtypes IMPC patients. Log-rank test was used to verify p value, and $p < 0.05$ means statistically significant.

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