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Original Article

Clinicopathologic features and prognosis of triple-negative breast cancer in China: a retrospective cohort study of patients under 35 years old

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Abstract: Aim: To analyze factors that affect the prognosis of triple-negative breast cancer patients under 35 years old. Material and methods: We retrospectively analyzed confirmed triple-negative breast cancer cases from 2000 to 2016 in multiple institutions. A total of 105 patients were included in the study, Nineteen of them were diagnosed with age ≤ 25, and 86 of them were aged between 26 to 35. Result: There were no statistically significant differences in clinicopathologic features and treatment choices between patients aged ≤ 25 years and those aged 26-35 years ($P > 0.05$). Survival analysis showed no statistically significant differences in DFS and OS between the two groups ($P > 0.05$). Multiple factor analysis showed that age of menarche (HR 0.697, 95% CI [0.5634, 0.8631]), pregnancy correlation (HR 2.673, 95% CI [1.1581, 6.1741]), and lymph node positivity (HR 4.915, 95% CI [2.3774, 10.1627]) were independent prognostic factors that affected patients' DFS. Independent prognostic factors that influenced OS were age of menarche (HR 0.598, 95% CI [0.462 6, 0.775]) and lymph node positivity (HR 7.751, 95% CI [2.923, 20.559]). Conclusion: There was no difference in the clinicopathological features and prognosis between women ≤ 25 and women aged 26-35 years with triple-negative breast cancer. Age of menarche, pregnancy correlation, and positive lymph nodes were independent factors affecting prognosis. The relationship between reproductive factors and prognosis in young patients with triple-negative breast cancer needs further discussion.

Keywords: Triple-negative breast, young age breast cancer, breast-conserving therapy, clinicopathologic feature, prognosis

Introduction

Young age breast cancer makes up 26% of the triple-negative breast cancers (TNBC) [1]. TNBC is a breast cancer subtype that lacks estrogen (ER, PR) receptors and human epidermal factor growth receptor-2 (HER-2) expression, which accounts for 15%~20% of all breast cancers. Since there is no specific therapeutic target, triple-negative breast cancer has a poorer prognosis than other subtypes. However, due to the internal heterogeneities, some subtypes of triple-negative breast cancer may have a good prognosis even without adjuvant therapy [2]. Young age breast cancers show the same aggressive biology, and usually with a higher T stage and more lymph node positivity. Previous studies have classified young age breast cancer into the ages of 30, 35, and 40. In recent years, ST-Gallen guidelines have defined breast cancer diagnosed under the age of 35 years as "very young age breast cancer". According to statistical results from SEER, the tumor source of young adult aged over 25 with cancer transforms from non-epithelial tumor to epithelial tumor. Breast cancer only accounts for 2% of young adult cancer patients between 20 and 24 years old, while breast cancer which occurs over the age of 25 accounts for 8% [3]. This result suggests that breast cancers which occur before 25 years old and after 25 years old may have different etiologies and biological characteristics. The current studies have compared the difference between patients with tri-

ple-negative breast cancer under 35 years old and patients older than 35 [3-5]. Internal differences in triple-negative breast cancer under 35 years of age have not been reported. In this study, the samples were divided into two age groups, ≤ 25 years and 26-35 years, to preliminarily explore the clinical characteristics and prognosis differences of patients with triple-negative breast cancers under 35 years, and analyze the factors affecting the prognosis of triple-negative breast cancer diagnosed under the age of 35.

Materials and methods

Source of data

We retrospectively analyzed clinical data of female triple-negative breast cancer patients diagnosed under the age of 35 from January 1, 2000 to December 31, 2016 in the First People's Hospital of Anqing City, the First People's Hospital of Zhaoqing City, the Third Affiliated Hospital of Guangzhou Medical University, and the Hezhou People's Hospital. We ruled out patients with a history of malignancy, incomplete clinical data, and loss to follow-up. A total of 105 patients were included in the study, including 19 patients (younger age group) with the age of diagnosis ≤ 25, and 86 patients (older age group) aged 26-35. Our research was approved by the ethical boards of the First People's Hospital of Anqing City, Anqing, China.

Research method

We compared the clinical pathology and prognosis of the two age groups, including the prognosis of the two age groups under different surgical methods. The single-factor analysis was used to identify clinical and pathological feature factors that influenced the prognosis. Then, independent prognostic factors were screened by adjusted multivariate analysis. A subgroup analysis was conducted according to the results of the multi-factor analysis to further analyze the differences in prognosis and characteristics among relevant factors.

Diagnostic criteria

We classified the stage of the prognosis according to the 8th edition American Joint Committee on Cancer (AJCC) cancer staging system [6], in which the stage of T, M, and N are pathological staging. Patients were diagnosed with triple-negative breast cancer based on the immunohistochemical staining results. Patients with negative ER and PR results, negative HER-2 results, or negative FISH test results were identified to have triple-negative breast cancer.

Statistical method

To compare the clinicopathological characteristics, treatment plan, and metastasis of patients aged ≤ 25 years and those aged 26-35 years, we applied the Chi-square test to assess the categorical variables and adjusted them by Fisher's exact test and Yates Correction. The disease-free survival rate (DFS) and overall survival rate (OS) were calculated by the Kaplan-Meier method. The difference in the survival curve was evaluated by the Log-rank test. The Cox proportional hazards model was used for multivariate analysis. All analyses were performed using R language packages. $P < 0.05$ was considered statistically significant.

Results

Comparison of clinicopathological features between two age groups

There were no statistically significant differences between the two age groups in terms of age of menarche, family history, pregnancy correlation, lymph node-positive status, tumor size, TNM stage, pathological type, histological grade, and prognosis stage ($P > 0.05$), as shown in **Table 1**.

Comparison of treatment methods between two age groups

There were no statistically significant differences between the two age groups in the use of chemotherapy regimen, neoadjuvant chemotherapy, or radiotherapy ($P > 0.05$). In the vein of the surgical methods, 16 patients (15.7%) chose breast-conserving surgery, among which 10 patients (62.5%) received postoperative radiotherapy, and 9 patients (56.3%) had the prognosis stage of T12N0. Patients aged ≤ 25 years were more likely to choose breast-conserving surgery, but there was no statistically significant difference from those aged 26-35 years ($P > 0.05$), as shown in **Table 2**.

Table 1. Comparison of clinicopathological features between the two age groups

Clinicopathologic features	Young group (n=19)	Senior group (n=86)	χ^2	P
Age of menarche (years)			5.489	0.064
≤ 12	7 (36.8)	13 (15.1)		
≥ 15	4 (21.1)	35 (40.7)		
13-14	8 (42.1)	38 (44.2)		
Family history			0.0019	0.793
No	17 (89.5)	76 (88.4)		
Yes	2 (10.5)	10 (11.6)		
Pregnancy correlation			0.324	0.907
No	18 (94.7)	76 (88.4)		
Yes	1 (5.3)	10 (11.6)		
Lymph node positive			0.090	0.765
Yes	9 (47.4)	44 (51.2)		
No	10 (52.6)	42 (48.8)		
Tumor size > 2 cm			0.026	0.872
Yes	12 (63.2)	56 (65.1)		
No	7 (36.8)	30 (34.9)		
T staging			2.990	0.559
Tis	1 (5.3)	3 (3.5)		
T1	5 (26.3)	22 (25.6)		
T2	8 (42.1)	48 (55.8)		
T3	5 (26.3)	11 (12.8)		
T4	0 (0)	2 (2.3)		
N staging			3.289	0.349
N0	10 (52.6)	42 (48.8)		
N1	6 (31.6)	19 (22.1)		
N2	3 (15.8)	13 (15.1)		
N3	0 (0)	12 (14.0)		
Prognosis staging			2.223	0.528
0	1 (5.3)	3 (3.5)		
1	2 (10.5)	16 (18.6)		
2	8 (42.1)	23 (15.1)		
3	8 (42.1)	44 (51.2)		
Pathological type			0.436	0.793
Carcinoma in situ	3 (15.8)	9 (10.5)		
Invasive cancer	16 (84.2)	77 (89.5)		
Histological grading			1.008	0.604
I	1 (5.3)	3 (3.5)		
II	10 (52.6)	36 (41.9)		
III	8 (42.1)	47 (54.7)		

Survival condition

In the follow-up period, 30 patients (28.6%) had a recurrence and metastasis, and 23 of them (21.9%) died due to the recurrence and metastasis. The 3-year survival rate was 73%. The 5-year survival rate was 66.5%. The median survival was 5.78 years. The median disease-free survival (DFS) was 5.35 years. There was no significant difference in DFS (3-year DFS: 63.2% vs 74.2%, P=0.34) and OS (3-year OS: 63.2% vs 83.6%, P=0.25) between the younger age group and the older age group (P > 0.05). See **Figures 1** and **2**. There was no statistically

Table 2. Comparison of treatment methods between the two age groups

Treatment	Young group (n=19)	Senior group (n=86)	χ^2	P
Operation method			4.796	0.066
Mastectomy	13 (68.4)	76 (88.4)		
Breast conserving surgery	6 (31.6)	10 (11.6)		
Chemotherapy			11.078	0.086
AC	3 (15.8)	2 (2.2)		
AC-T	5 (26.3)	27 (30.0)		
AT	1 (5.3)	15 (16.7)		
CEF	2 (10.5)	14 (15.6)		
TAC	1 (5.3)	13 (14.4)		
Others	4 (21.2）	13 (14.4)		
No treatment	3 (15.7)	6 (7.4)		
Neoadjuvant therapy			1.523	0.356
Yes	2 (10.5)	20 (23.3)		
No	17 (89.5)	66 (76.7)		
Radiotherapy			1.131	0.410
Yes	2 (10.5)	19 (22.1)		
No	17 (89.5)	67 (77.9)		

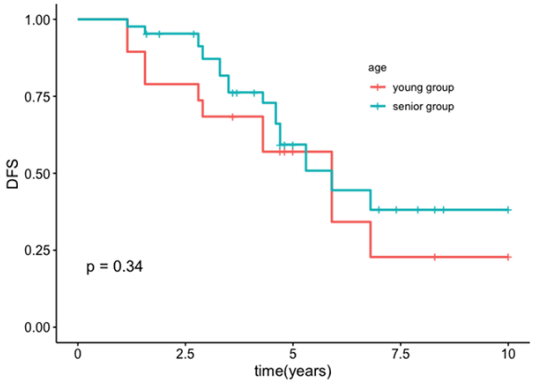

Figure 1. DFS curve of two age groups.

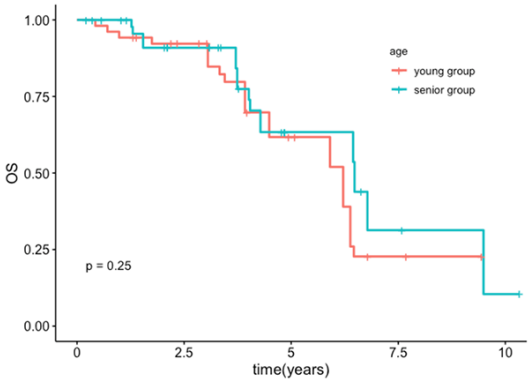

Figure 2. OS curve of two age groups.

significant difference in DFS or OS between the mastectomy group and the breast-conserving surgery group (P > 0.05), as shown in **Figures 3** and **4**.

Comparison of metastasis between two age groups

Among patients with postoperative metastasis, there was no significant difference between the two age groups (χ^2=1.217, P=0.749), see **Table 3**.

Analysis of prognostic factors

As TMN staging and prognostic staging have a linear relationship with prognosis, they were not included in the univariate analysis. Univariate analysis of 105 patients showed that the age of menarche, positive lymph node, and pregnancy correlation were associated with prognosis. Irrelevant factors included age of diagnosis, family history, height, body mass, surgical method, pathological type, tumor size, histological grade, and whether they had received radiotherapy and neoadjuvant therapy, as shown in **Tables 4** and **5**. Cox multivariate analysis showed that the age of menarche, positive lymph nodes, and pregnancy correlation were independent prognostic factors affecting DFS, while the age of menarche and positive lymph nodes were independent prognostic factors affecting OS (P < 0.05). Age of

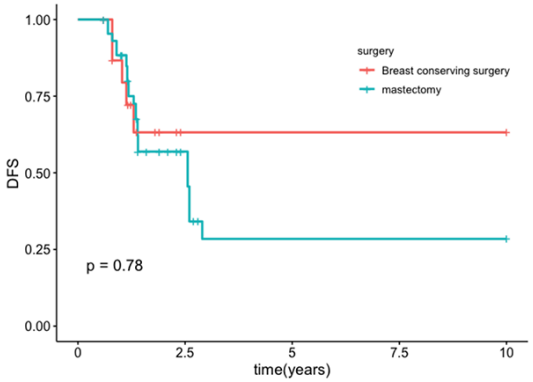

Figure 3. DFS curve of different surgical methods.

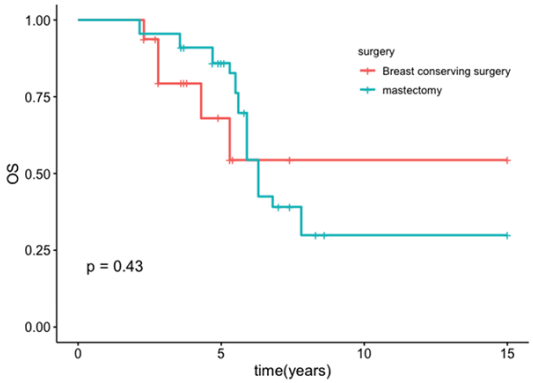

Figure 4. OS curve of different surgical methods.

diagnosis and surgical methods were not related to prognosis, as shown in **Tables 6** and **7**.

Subgroup analysis

We divided participants into three age groups (≤ 12 years old, 13-14 years old, and ≥ 15 years old) according to the age of menarche. Comparing the survival curves of the three groups, the DFS, and OS of patients with the age of menarche ≤ 12 years were significantly lower than the other groups (DFS: P < 0.0001; OS: P=0.0061), as shown in **Figures 5** and **6**. There was no significant difference in DFS or OS between the age group of 13-14 years and ≥ 15 years (DFS: P=0.24; OS: P=0.42). We found no difference in clinicopathologic factors among the three subgroups (P > 0.05), see **Table 8**.

Discussion

Prognostic factors

It is generally accepted that the prognostic factors of TNBC are tumor size and lymph node metastasis. Rakha et al. [7] conducted a long-term follow-up (median follow-up period: 56 months) on 282 TNBC patients and found that tumor size, lymph node stage, and androgen receptor status were the most significant prognostic markers. In a study in China, Yuan et al. [8] reviewed 305 TNBC patients, and the multivariate Cox regression analysis showed that tumor size and lymph node status were independent factors affecting the prognosis of patients. The results further confirmed that the existing views, lymph node-positive effect in the multiple factors analysis of patients were independent prognostic factors for DFS and OS.

There is much controversy about the influence of age on the prognosis of triple-negative breast cancer. Some studies believe that younger patients with triple-negative breast cancer have a worse prognosis than older patients [4, 5, 9]. Cancello et al. [10] divided breast cancer patients into three groups of < 25 years old, 25-29 years old, and 30-34 years old for analysis. There was no difference in the distribution of molecular typing and prognosis among the three age groups. In this study, DFS and OS analysis were performed on patients with triple-negative breast cancer ≤ 25 years old and 26-35 years old, and no difference was found in prognosis between the two groups. In addition, age was not found to be a prognostic factor in the multivariate analysis. Breast cancer patients under 25 years old, especially those with the three-negative subtype, are relatively rare. No studies have been conducted on patients under 25 years old with the three-negative subtype. However, combined with the conclusions of the previous similar studies, it suggests that although there may be a linear correlation between age and the prognosis of TNBC, there may not be such a trend in the younger population (≤ 35 years old).

The biological behavior of TNBC and its high mortality rate may influence the choice of surgical procedures for health professionals and patients. Many studies have shown that a larger surgical scope does not bring more benefits to TNBC patients. Li Yun et al. [11] analyzed 618 patients undergoing breast-conserving surgery and found that breast-conserving surgery would not increase the risk of local recurrence and death of TNBC. It has been reported that breast-conserving surgery will not reduce

Table 3. Comparison of metastases between the two age groups

Group	Number	LRR	DM	LRR+DM	CBC
Young group	3	1 (33.3)	2 (66.7)	0 (0)	0 (0)
Senior group	27	6 (22.2)	13 (48.1)	4 (14.8)	4 (14.8)
χ^2			1.217		
P			0.749		

Note: LRR, local recurrence; DM, distant metastasis; LRR+DM, local and distant metastasis; CBC, contralateral breast cancer.

Table 4. Univariate analysis of DFS in TNBC patients under 35 years old

Factor	HR (95% CI)	β	Wald	P
Age	0.7066 (0.3379~1.4774)	-0.3473	-0.9228	0.3561
Family history	0.9590 (0.3771~2.4389)	-0.0419	-0.0880	0.9299
Menarche age	0.2336 (0.1060~0.5145)	1.4543	-3.6093	0.0003
height	1.0254 (0.9634~1.0913)	0.0251	0.7885	0.4304
Body mass	1.0211 (0.987~1.0559)	0.0209	1.2235	0.2212
Operation method	0.8391 (0.3536~1.9913)	-0.1754	-0.3978	0.6908
Tumor size > 2 cm	2.0108 (0.9903~4.0829)	0.6985	1.9331	0.05323
Lymph node positive	4.8673 (2.384~9.9337)	1.5825	4.3478	0.0001
pathologic types	1.4769 (0.455~4.7910)	0.3900	0.6495	0.5160
Treatment options	0.4108 (0.0918~1.8394)	-0.8896	-1.1632	0.24477
Histological grading	1.4970 (0.1974~11.3532)	0.4035	0.3903	0.6963
Pregnancy correlation	3.7423 (1.6415~8.5320)	1.3197	3.1386	0.0017

Table 5. Univariate analysis of OS in TNBC patients under 35 years old

Factor	HR (95% CI)	β	Wald	P
Age	0.5682 (0.2563~1.2597)	-.05652	-1.3916	0.1641
Family history	1.0051 (0.3537~2.8561)	0.0051	0.0095	0.9924
Menarche age	0.6316 (0.4969~0.8029)	-0.4594	-3.7537	0.0002
height	1.0288 (0.9599~1.1026)	0.0284	0.8023	0.4224
Body mass	1.0151 (0.9769~1.0548)	0.0150	0.7674	0.4429
Operation method	0.8985 (0.3476~2.3226)	-0.1070	-0.2208	0.8252
Tumor size > 2 cm	2.2842 (0.9942~5.2480)	0.8260	1.9463	0.0516
Lymph node positive	7.2906 (2.8155~18.879)	1.9866	4.0923	0.0001
pathologic types	1.0345 (0.3161~3.3859)	0.0339	0.0561	0.9553
Treatment options	0.3278 (0.0717~1.4996)	-1.1152	-1.4376	0.1505
Histological grading	0.8904 (0.1127~7.0375)	0.1161	-0.1101	0.9123
Pregnancy correlation	4.3702 (1.876~10.1771)	1.4748	3.4195	0.6273

the survival and overall survival of TNBC patients without local recurrence [12]. A review of 1930 patients with TNBC I~III period prognosis research shows that although patients with age < 40 years have a higher local recurrence rate (6.4% vs 4.5%, P=0.06) compared with patients ≥ 40 years, the multivariate analysis showed no correlation between operation style and age with local or distant recurrence [13]. Multivariate analysis in this study showed that the surgical approach was not a prognostic factor for patients that affect DFS and OS. Compared with the age factor, the prognosis of TNBC is more likely to be affected by its biological characteristics. The use of systemic adjuvant therapy can effectively improve the prognosis of TNBC and provide breast-conserving therapy for young patients with triple-negative breast cancer after comprehensive risk assessment, which may improve the life quality and psychological status of patients.

Table 6. Multivariate analysis of DFS in TNBC patients under 35 years of age

Factor	HR (95% CI)	β	Wald	P
Menarche age	0.6974 (0.5634~0.8631)	-0.3605	-3.312	0.0009
Pregnancy correlation	2.6739 (1.1581~6.1741)	0.9836	2.304	0.0212
Lymph node positive	4.9154 (2.3774~10.1627)	1.5924	4.297	< 0.001

Table 7. Multivariate analysis of the effects of TNBC on OS in patients under 35 years of age

Factor	HR (95% CI)	β	Wald	P
Menarche age	0.5988 (0.462~0.775)	-0.5129	-3.897	0.0001
Pregnancy correlation	2.3052 (0.973~5.456)	0.8351	1.900	0.0575
Lymph node positive	7.7519 (2.9230~20.559)	2.0429	4.115	0.0001

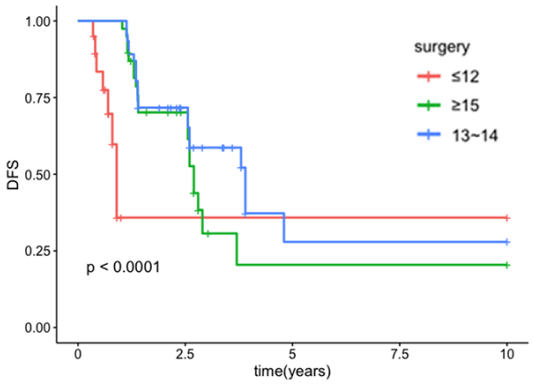

Figure 5. DFS curves of age of menarche in three groups.

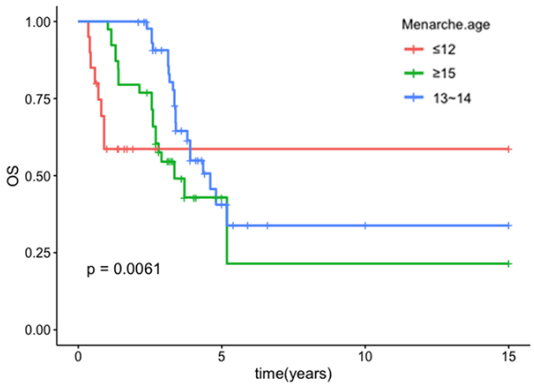

Figure 6. OS curve of three groups of menarche age patients.

A special type, common in young age cancer patients, is pregnancy-associated breast cancer (PABC). Due to the hyperemia of the breast in pregnancy and lactation, the tumor is often overlooked at the early stage of the disease. Patients usually have a high local stage of diagnosis due to delayed consultation. Several pieces of literature have described that PABC is more likely to show poor pathological characteristics, such as large tumor size and negative estrogenic receptor, and tends to have poorer prognosis [14, 15]. PABC is traditionally defined as breast cancer diagnosed during pregnancy and one year after delivery. A recent study with a large sample size evaluated the prognosis of 778 patients with PABC and found that compared with non-PABC patients, patients diagnosed with PABC, especially within 1 year after delivery, had higher TN staging and were more likely to be TNBC phenotype [16]. A meta-analysis of 3628 patients showed that PABC patients had a higher risk of death and recurrence compared with non-pregnancy-related breast cancer patients. This trend was more pronounced in postpartum breast cancer patients (pHR: 1.84, 95% CI 1.28-2.65) compared with patients diagnosed during pregnancy (pHR: 1.29, 95% CI 0.74 to 2.24) [17]. Due to the limited sample size, this study did not distinguish between postpartum breast cancer and gestational breast cancer in PABC patients, but among 11 pregnancy-related breast cancer patients, 8 (72.7%) were diagnosed within 1 year after delivery. Herein, the multi-factor analysis showed that pregnancy correlation was an independent prognostic factor affecting DFS and OS in patients under 35 years old, which added evidence to the previous conclusions.

In this study, patients with age of menarche ≤ 12 years old accounted for 19%. There was no difference in the distribution between the two age groups. We divided patients into three subgroups based on the age of menarche and compared the survival curves of the three groups.

Table 8. Comparison of characteristics among three groups of menarche age patients [case (%)]

Group	Family history		Pregnancy correlation		Tumor size > 2 cm		Positive lymph node	
	No	Yes	No	Yes	No	Yes	No	Yes
≤ 12 years old	17 (85.0)	3 (15.0)	16 (80.0)	4 (20.0)	5 (28.6)	15 (71.4)	7 (35.0)	13 (65.0)
13-14 years old	42 (33.3)	4 (66.7)	43 (93.5)	3 (6.5)	12 (25.0)	34 (75.0)	23 (50.0)	23 (50.0)
≥ 15 years old	34 (87.2)	5 (12.8)	37 (94.9)	2 (5.1)	14 (36.6)	2525 (61.8)	22 (56.4)	17 (43.6)
χ^2	0.666		4.170		1.219		2.432	
p	0.717		0.124		0.544		0.296	

The DFS and OS of patients with age of menarche ≤ 12 years were significantly lower than those of the other two groups. Multivariate analysis showed that the age of menarche was an independent prognostic factor for DFS and OS. We compared the pathological characteristics of the three groups and found that patients with age of menarche ≤ 12 years old had a large proportion of positive lymph nodes. The difference was not statistically significant, suggesting that there may be an interaction between the age of menarche and lymph node status. The relationship between age of menarche and prognosis should be further investigated by studies with larger sample size. At present, few studies have reported the relationship between estrogen exposure-related factors such as the age of menarche and the prognosis of breast cancer. The conclusions of existing studies are different. Song et al. [18] reported that, longer estrogen exposure in patients with ER+, PR+, and HR+HER2+ showed better disease-free survival (HR=0.97, 95% CI=0.96~0.99). Older age at menarche (OS=1.10, 95% CI=1.03-1.19) was associated with poorer survival. A small sample study conducted by Daha et al. [19] pointed out that patients with positive HER-2 and TNBC were related to the younger age of menarche, and the age of menarche was moderately correlated with lower survival rate. Development mechanism of estrogen to three negative breast cancer is unclear. Speculation is that early menarche age often associated with earlier breast development, which increases the window period of breast tissue exposing to the carcinogenic factors, resulting in an increased risk of breast cancer in patients who have TNBC-related risk factors [20]. As to the role of estrogen in the development of triple-negative breast cancer, Yu et al. [21] found that the expression rate of GPER in ER-negative breast cancer was 62.5% and was negatively correlated with ER and PR. They also investigated the influence of blocking estrogen/G protein coupling of estrogen receptor (GPER) pathway mediated signaling to the base for group TNBC cell viability and motility among TNBC patients and found that estrogen/GPER pathways mediating the rapid activation of ERK1/2 phosphorylation, thereby enhancing the cell proliferation, cell survival, and cell migration/invasion ability. A prospective study by Vihko et al. [22] observed the relationship between the age of menarche and estrogen level in 200 women from 7 to 17 years old. The study followed participants for 5 years and found that even if in the adulthood of the participants, the estrogen level in women with age of menarche < 13 years old was twice as high as that in other groups. This suggests that the adverse effect of the age of menarche on prognosis may be due to the combination of high estrogen status and estrogen-associated receptors in adults. In addition, Liu et al. [23] analysed the expression of cyclin D1 (CCND1) in TNBC patients and found that GG genotype of CCND1 was deficient in patients with menarche earlier than 12.2 years old (OR= 0.61, 95% CI=0.42-0.87, P=0.0241), menopause earlier than 49 years old (OR=0.57, 95% CI=0.39-0.82, P=0.0093), and triple-negative breast cancer (OR=0.28, 95% CI=0.13~0.62, P=0.0006). CCND1 plays a priming role in the cell cycle. The copy number frequency of CCND1 in the three-negative breast cancer samples was higher than that of other breast cancers [24-26], suggesting that TNBC, early age of menarche and other factors related to poor prognosis may have a common mechanism. With the improvement of people's living standards, early menarche has become a universal phenomenon. It is necessary to pay more attention to the relationship between age of menarche and breast cancer, so as to provide more guidance for disease prevention and clinical practice.

Advantages and limitations

No previous studies have described the incidence of triple-negative breast cancer before the age of 25. In this study, we retrospectively analyzed the internal differences among patients diagnosed with triple-negative breast cancer before the age of 35, to supplement the current evidence on the clinical characteristics of young triple-negative breast cancer, especially the relationship between reproductive factors and prognosis. The weakness of this study was that compared with breast cancer patients under the age of 35, patients with triple-negative breast cancer were a small subset with small sample size. Patients with incomplete data due to loss of follow-up were excluded, resulting in a relatively small sample size of the study. The age of menarche in the study was based on the recall of patients, which may have led to the misclassification. It is worth conducting multi-center and larger sample studies in the future to further explore and analyze the characteristics and prognosis of young triple-negative breast cancer.

Disclosure of conflict of interest

None.

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