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Expression of mammalian sterile 20-like kinase 1 and 2 and Yes-associated protein 1 proteins in triple-negative breast cancer and the clinicopathological significance

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Abstract

Background and aim: Mammalian sterile 20-like kinase 1 and 2 (MST1/2) and Yes-associated protein 1 (YAP1) are the core molecules of the Hippo signaling pathway, which have been found to be unbalanced in the occurrence of tumors and promote the development of the lesions. The present study aimed to investigate the expression of MST1/2 and YAP1 proteins in triple-negative breast cancer (TNBC) and their clinicopathological significance.

Methods: Immunohistochemistry was used to detect the expression level of protein in tissues. According to the percentage of positive cells and staining intensity, the expression intensity of MST1/2 and YAP1 proteins in the tissue samples was scored, and the correlation between MST1/2 and the clinicopathological features of TNBC were discussed.

Results: The expression of MST1/2 and YAP1 was associated with histological grade, metastasis, lymph node metastasis stage, and tumor node metastasis stage. The overexpression of YAP1 predicted a poor prognosis in terms of overall survival and disease-free survival time. The MST1/2 expression was associated with improved overall survival and disease free survival of the patients.

Conclusion: MST1/2 and YAP1 may be used as prognostic indicators to evaluate the recurrence of TNBC and might become one of the new targets for breast cancer treatment.

Abbreviations: DFS = disease free survival, LNM = lymph node metastasis, MST1/2 = mammalian sterile 20-like kinase 1 and 2, OS = overall survival, TNBC = triple negative breast cancer, TNM = tumor node metastasis, YAP1 = Yes-associated protein 1.

Keywords: disease free survival, mammalian sterile 20-like kinase 1 and 2, overall survival, triple-negative breast cancer, Yes-associated protein 1

1. Introduction

Breast cancer is a malignant tumor in the mammary epithelium or ductal epithelium. The etiology and pathogenesis of breast cancer are complex and have not yet been fully elucidated, but many high-risk factors, such as family history, breast cancer-related genes, reproductive factors, sex hormones, and environmental factors, might be related to breast cancer.[1,2] With the accumulation of high-risk factors, the risk of breast cancer increased. The incidence of breast cancer among female cancers worldwide is 24.2%, and the mortality rate is 15%, ranking first, of which 52.9% occurs in developing countries.[3] In China, >300,000 women are diagnosed with breast cancer every year, especially in the eastern coastal and economically developed areas.[4] According to the expression of receptors, breast cancer can be divided into 3 types: hormone receptor-positive breast cancer, epidermal growth factor receptor 2 positive breast cancer, and triple-negative breast cancer (TNBC). Compared with the other 2 types of breast cancer, TNBC presents the clinical characteristics of high recurrence rate, high mortality, and strong invasion. Presently, limited treatment methods are available, and the prognosis is poor.[5,6]

Hippo signal is a highly conservative signaling pathway for regulating growth, detected in *Drosophila* for nearly 20 years. It plays a key role in regulating organ size and maintaining the balance of cell proliferation, apoptosis, and maintaining the stability of the internal environment.[7,8] The core of the Hippo signaling pathway is a protein kinase cascade reaction, mainly composed of mammalian sterile 20-like 1 and 2 (MST1/2), Sav1, large tumor suppressor 1 and 2 (LATS1/2), and Yes-associated protein 1 (YAP1) in mammals.[9,10] The mutation of any element in most Hippo pathways causes tissue overgrowth, and the Hippo signaling pathway also plays a role in the gastrointestinal

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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tissues of mammals. Moreover, YAP1 is associated with the protein molecules of Hippo signaling pathway and the downstream physiological effects.[11] Some studies have shown that YAP1 is an oncogene in breast cancer, and its overexpression promotes the proliferation and migration of breast cancer cells.[12,13] While MST1/2 is a Hippo homologous protein existing in mammalian cells, and its activity in cells is similar to that in *Drosophila*, it is first activated under physiological or non-physiological stress conditions, causing phosphorylation of the downstream gene *LATS1/2*, while downstream effector proteins, YAP and TAZ, are activated and degraded by related proteases in the cytoplasm, thereby inhibiting excessive cell growth.[14,15]

Typically, MST1/2 and YAP1 are closely related to the occurrence and development of various tumors. In this study, the expression of MST1/2 and YAP1 in TNBC was detected, for the first time by immunohistochemical staining, and the correlation between the expression of MST1/2 and YAP1 and the clinicopathological factors of TNBC was discussed. Also, the related prognosis was analyzed to obtain novel ideas for the treatment of breast cancer.

2. Methods

2.1. Patients and tissue samples

A total of 112 TNBC tissues were collected from the Department of Pathology, Suzhou Hospital of Anhui Medical University (Suzhou Municipal Hospital of Anhui Province, China), from January 2009 to December 2015. All patients presented complete clinical, pathological, and follow-up data but no distant metastasis before the surgery. Patients who received preoperative chemotherapy, radiotherapy, targeted therapy, or endocrine treatment were excluded from this study. The age of the patients was 26 to 77 (median age, 55.3) years. The overall survival (OS) was calculated from surgery to death; data from patients who died from disease unrelated to TNBC, accident, and those who were lost to follow-up in December 2015 were censored (mean survival time: 42.21 [range, 6–67] months). Disease free survival (DFS) was calculated from diagnosis to a regional recurrence or distant metastasis. The histological grade was defined according to the World Health Organization (WHO) Classification of Breast Tumors, 4th Edition (2012). The other clinicopathological characteristics are listed in Table 1. This study was approved by the Ethics Committee of Suzhou Hospital of Anhui Medical University (Suzhou Municipal Hospital of Anhui Province) and conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Table 1

Patients characteristics.

Patients characteristics	Frequency (n)	Percentage (%)
Ages		
<40 y	43	38.4
≥40 y	69	61.6
Size, cm		
<2.0	44	39.3
≥2.0, <5.0	58	51.8
≥5.0	10	5.9
Menopausal status		
Premenopausal	45	40.2
Postmenopausal	67	59.8
Histopathology		
Intraductal carcinoma	2	1.8
Invasive ductal carcinoma	85	75.9
Invasive lobular carcinoma	6	5.3
Other types	19	17.0
Metastasis		
Absent	95	84.8
Present	17	15.2
Adjuvant chemotherapy		
Yes	19	17.0
No	93	83.0
Histology grade		
Well	44	39.3
Moderate	55	49.1
Poor	13	11.6
LNM stage		
Negative	65	58.0
1–3	33	29.5
4–9	10	8.9
>9	4	3.6
TNM stage		
I	39	34.8
II	50	44.6
III	23	20.5

LNM = lymph node metastasis, TNM = tumor node metastasis.

2.2. Immunohistochemical analysis

All specimens were fixed in 10% buffered formalin, embedded in paraffin, and sliced (4-μm-thick sections). The sections were then deparaffinized and rehydrated with xylene and graded alcohol, followed by washing in phosphate-buffered saline (PBS, pH 7.2) for 10 minutes. The endogenous peroxidase activity was blocked by incubation in 3% H_2O_2 at room temperature for 10 minutes and heated to 95°C for 30 minutes for antigen retrieval. Subsequently, the sections were blocked with goat serum and incubated with MST1/2 (dilution 1:100, ab87322, Abcam) and YAP1 (dilution1:50, ab52771, Abcam) primary antibodies at 4 °C overnight. Subsequently, the slides were incubated with polymer enhancer (reagent A) and goat anti-mouse antibody (reagent B) and developed using freshly prepared 3,3′-diaminobenzidine (DAB) substrate. Finally, the sections were counterstained with hematoxylin, dehydrated, air-dried, and mounted. PBS replaced the primary antibody that served as the negative control, and the corresponding protein-positive slice was a positive control.

2.3. Evaluation of immunostaining

All slides were evaluated by 2 experienced pathologists blinded to the clinical data or the disease outcome. The immunostaining determined that MST1/2 and YAP1 were localized to the cytoplasm in 10 fields (×400 magnification). To evaluate MST1/2 and YAP1 expression, the staining of the entire carcinoma-involved area was graded in terms of extent and intensity. The intensity of the staining was divided into 4 grades: 0, none; 1, weak; 2, moderate; 3, strong. The extent of staining was also divided into 5 categories: 0, ≤5%; 1, 6% to 25%; 2, 26% to 50%; 3, 51% to 75%; 4, 76% to 100%. Finally, we determined the score by multiplying the intensity and the extent of staining to generate immunostaining scores from 0 to 12. The immunostaining was considered positive when the scores were ≥3.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 22.0 software for Windows (IBM, New York, NY). Fisher exact or Pearson chi-

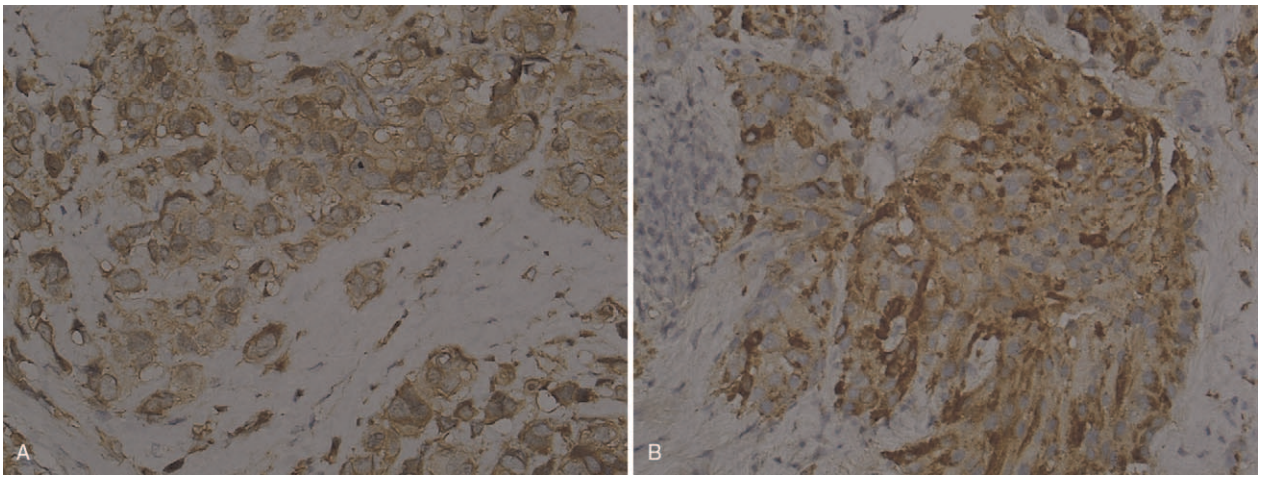

Figure 1. Immunostaining of MST1/2 and YAP1 in TNBC. A, Positive staining of MST1/2 in TNBC (100 magnification); scale bar, 100 μm. B, Positive staining of YAP1 in TNBC (100 magnification). MST1/2 = mammalian sterile 20-like kinase 1 and 2, TNBC = triple negative breast cancer, YAP1 = Yes-associated protein 1.

square test were used to analyze the correlation between protein expression and clinicopathological indices. The correlation between the expression of these factors was evaluated by Spearman correlation analysis. The univariate survival analysis of OS and DFS was based on the Kaplan–Meier method with log-rank tests. A multivariate Cox regression model was used to analyze the influence of various factors on OS and DFS. β-coefficients and 95% confidence intervals (CI) were used for analysis. $P < .05$ indicated statistical significance.

3. Results

3.1. Expression of MST1/2 and YAP1 in TNBC

In the present study (Fig. 1A and B), MST1/2 and YAP1 proteins were expressed in 33.0% and 54.5% of TNBC.

3.2. Correlation of MST1/2 and YAP1 expression with clinicopathological characteristics in TNBC patients

A correlation was established between MST1/2, YAP1 expression, and age and tumor size ($P > .05$). The expression of MST1/2 and YAP1 was associated with histological grade, metastasis, lymph node metastasis (LNM) stage, and tumor node metastasis (TNM) stage ($P < .05$). See Table 2 for details.

3.3. Correlations among MST1/2, YAP1, and LNM stage in TNBC

A negative correlation was established between MST1/2 and YAP1 expression ($R^2 = 0.101$, $P = .001$). Furthermore, YAP1 was positively correlated with LNM stage ($R^2 = 0.070$, $P = .005$). The expression of MST1/2 showed a significantly negative correlation with the LNM stage ($R^2 = 0.038$, $P = .040$). See Fig. 2A–C for details.

3.4. Survival analysis

In the univariate analysis, OS and DFS were significantly correlated with clinicopathological factors, including histological grade, metastasis, LNM, and TNM stage. See Table 3 for details. The overexpression of YAP1 predicted a poor prognosis with respect to OS and DFS (log-rank = 88.796 and 79.044, respectively; $P < .001$). MST1/2 expression was associated with a high OS and DFS of the patients (log-rank = 27.336 and 24.639, respectively; $P < .001$). See Fig. 3A–D for details.

The multivariate analysis included variables, such as age, tumor size, histological grade, metastasis, LNM stage, TNM stage, MST1/2 and YAP1 expression, the LNM stage, and TNM

Table 2

The correlation between YAP1, MST1/2, and clinicopathological characteristics in TNBC.

	YAP1			MST1/2		
Variable	**Negative**	**Positive**	***P***	**Negative**	**Positive**	***P***
Ages			.085			.683
<40 y	24	19		30	13	
≥40 y	27	42		45	24	
Size, cm			.582			.375
<2.0	21	23		25	19	
≥2.0, <5.0	27	31		45	13	
≥5.0	3	7		5	5	
Metastasis			.012			.043
Absent	48	47		60	35	
Present	3	14		15	2	
Histology grade			<.001			.004
Well	29	15		22	22	
Moderate	21	34		41	14	
Poor	1	12		12	1	
LNM stage			<.001			.014
Negative	43	22		36	29	
1–3	5	28		29	4	
4–9	2	8		7	3	
>9	1	3		3	1	
TNM stage			<.001			<.001
I	29	10		16	23	
II	19	31		39	11	
III	3	20		20	3	

LNM = lymph node metastasis, MST1/2 = mammalian sterile 20-like kinase 1 and 2, TNM = tumor node metastasis, YAP1 = Yes-associated protein 1.

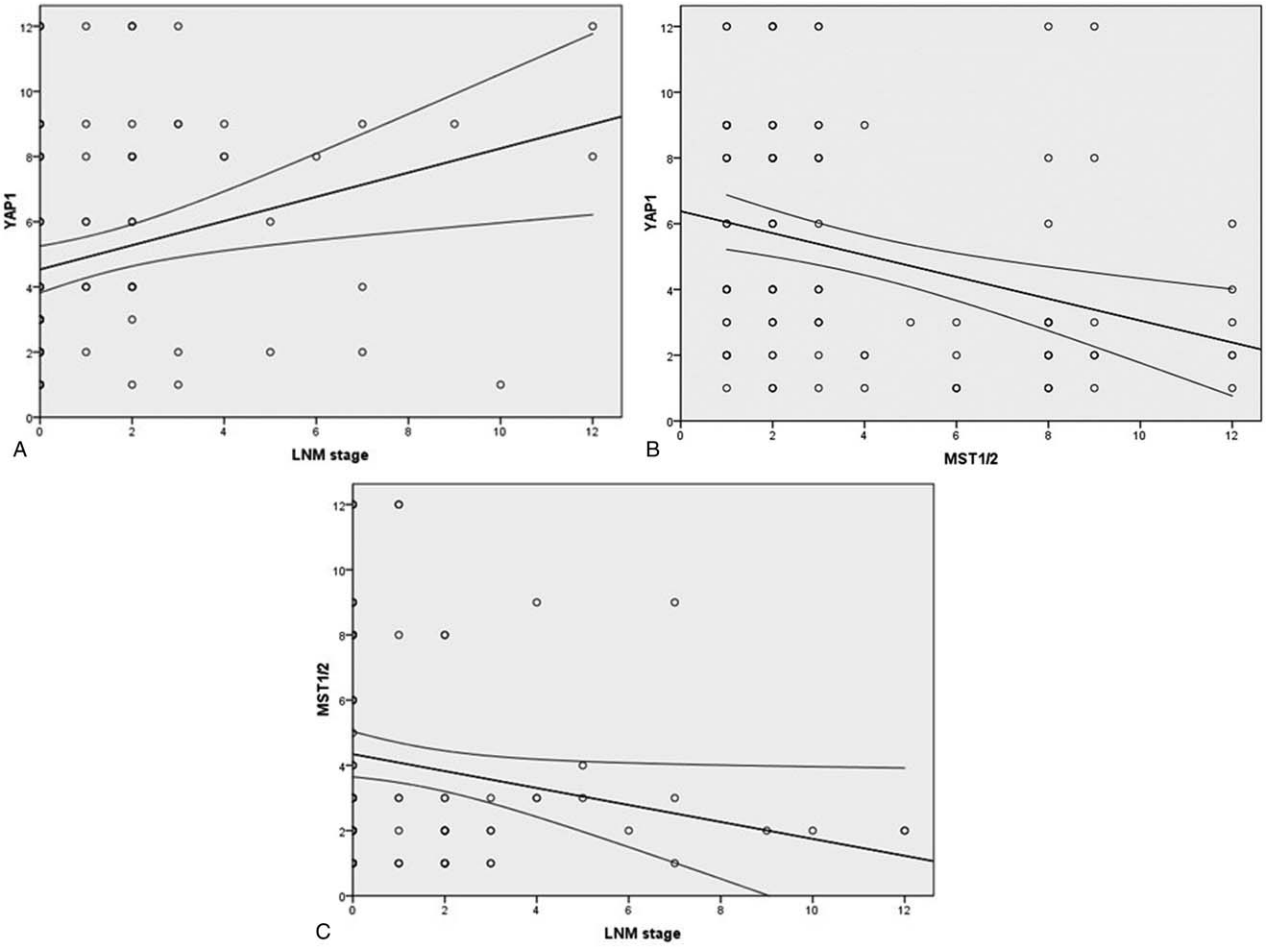

Figure 2. Correlations among MST1/2, YAP1, and LNM stage in TNBC. A, Negative correlation was established between MST1/2 and YAP1 expression (R2 = 0.101, *P* = .001); B, YAP1 was positively correlated with LNM stage (R2 = 0.070, *P* = .005); C, MST1/2 was significantly negative correlated with the LNM stage (R2 = 0.038, *P* = .040). LNM = lymph node metastasis, MST1/2 = mammalian sterile 20-like kinase 1 and 2, TNBC = triple negative breast cancer, YAP1 = Yes-associated protein 1.

stage, and MST1/2 and YAP1 expression, remained as independent prognostic factors of OS and DFS. See Table 4 for details.

4. Discussion

TNBC is the rarest molecular subtype of breast cancer, which usually affects younger patients. The tumor size is large, the grade is high, and the biological behavior is invasive. Although the study on this disease has made significant progress in tumor biology, and traditional cytotoxic chemotherapy is still the only available treatment for TNBC. To date, the clinical prognosis of TNBC is poor, and the overall median survival time of metastatic TNBC patients is only 18 months.[5,16,17] Related studies have shown that Hippo signaling pathway is highly

Table 3

Univariate regression model of prognostic covariates in TNBC patients.

	OS		DFS	
Variable	X^2	***P***	X^2	***P***
Age	2.780	.095	0.688	.407
Size	1.841	.398	2.137	.344
Histology Grade	2.582	.275	0.779	.677
metastasis	0.147	.702	9.363	.002
LNM	25.174	<.001	31.870	<.001
TNM	1.120	.571	9.321	.009
YAP1	11.419	<.001	8.554	.003
MST1/2	10.089	<.001	0.006	.938

DFS = disease free survival, LNM = lymph node metastasis, MST1/2 = mammalian sterile 20-like kinase 1 and 2, OS = overall survival, TNBC = triple negative breast cancer, TNM = tumor node metastasis, YAP1 = Yes-associated protein 1.

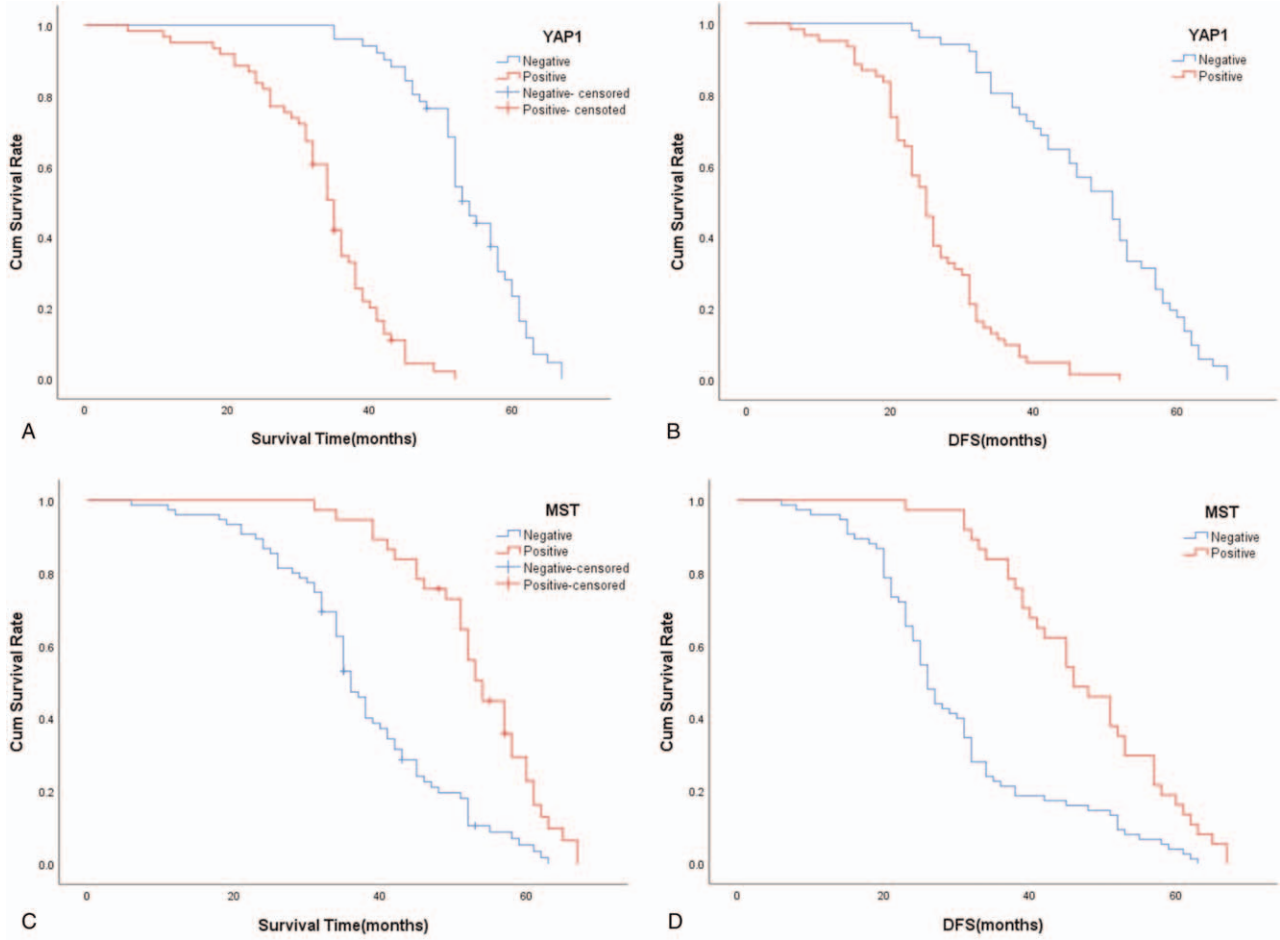

Figure 3. Kaplan–Meier analysis of the survival rate of patients with TNBC. A, The overexpression of YAP1 predicted a poor prognosis with OS (log-rank = 88.796, $P < .001$); B, The overexpression of YAP1 predicted a poor prognosis with DFS (log-rank = 79.044, $P < .001$); C, MST1/2 expression was associated with a high OS of the patients (log-rank = 27.336, $P < .001$); D, MST1/2 expression was associated with a high DFS of the patients (log-rank = 24.639, $P < .001$). MST1/2 = mammalian sterile 20-like kinase 1 and 2, OS = overall survival, TNBC = triple negative breast cancer, YAP1 = Yes-associated protein 1.

Table 4

Results of multivariate analyses of OS and DFS time.

Variable	Outcome	HR	*P*	95% CI	
Age	OS	0.245	.248	0.843	1.936
	DFS	–0.092	.807	0.436	1.907
Size	OS	–0.276	.108	0.542	1.062
	DFS	–0.270	.334	0.441	1.320
Histology Grade	OS	0.084	.678	0.731	1.621
	DFS	1.092	.019	0.135	0.837
metastasis	OS	1.524	.088	0.796	26.484
	DFS	3.387	<.001	3.728	34.606
LNM	OS	0.388	.022	1.057	2.055
	DFS	0.180	.521	0.691	2.073
TNM	OS	0.433	.024	1.059	2.245
	DFS	0.716	.061	0.968	4.329
YAP1	OS	2.104	<.001	4.019	16.716
	DFS	2.240	<.001	2.471	35.715
MST1/2	OS	–0.904	<.001	0.247	0.664
	DFS	–0.028	.006	0.479	1.974

DFS = disease free survival, LNM = lymph node metastasis, MST1/2 = mammalian sterile 20-like kinase 1 and 2, OS = overall survival, TNM = tumor node metastasis, YAP1 = Yes-associated protein 1.

activated in TNBC and plays a major role in tumor growth and metastasis.[18,19]

The inactivation of tumor metastasis suppressor genes has a critical role in the process of tumor cell metastasis. *MST1/2*, as a tumor metastasis suppressor gene, affects the phosphorylation of the factors related to the Hippo pathway, thus inhibiting tumor growth.[14,15] The results showed that as the upstream component of Hippo pathway, LATS1/2 could be activated, which in turn phosphorylates the transcription activator YAP1. Notably, phosphorylated YAP1 cannot enter the nucleus and is finally degraded by protease.[20] When the upstream component MST1/MST2 is knocked out, the kinase axis is inhibited, the dephosphorylated YAP1 is not degraded, and YAP1 accumulated in the cytoplasm is transferred to the nucleus, which leads to excessive growth and proliferation of cells.[21,22] The study by Britschgi et al[23] showed that YAP1 mediates the remarkable transformation of mammary epithelial cells, and LATS protein directly interacts with YAP1 to express LATS1 ectopically, which effectively inhibits the phenotype of YAP1 and delays the transformation, migration, and anchor growth of epithelial-mesenchymal cells. As a carcinogen, YAP1 is widely amplified in cancer cells, and its overexpression leads to a variety of tumors.[24–27]

In this study, immunohistochemistry results demonstrated that the positive expression rate of MST1/2 in TNBC tumor tissues was significantly lower than that in the corresponding non-tumor control tissues and negatively correlated with histological grade, TNM stage, and LNM stage. The results of Kaplan–Meier univariate survival analysis showed that the OS and DFS of patients with positive MST1/2 expression were significantly higher than those with negative MST1/2 expression. Compared with the results of MST1/2 expression, the positive expression rate of YAP1 in TNBC tumor tissue was significantly higher than that in the corresponding non-tumor control tissue and positively correlated with histological grade, TNM stage, and LNM stage. The results of Kaplan–Meier univariate survival analysis showed that the postoperative OS and DFS of TNBC patients with YAP1 positive expression were significantly shorter than those with YAP1 negative expression. The multivariate Cox regression analysis showed that the positive expression of MST1/2 and YAP1, TNM stage, and LNM stage were independent prognostic factors for survival of TNBC patients. These findings indicated that the downregulation or deletion of MST1/2 expression and the upregulation of YAP1 expression promote the progress and metastasis of TNBC, thus affecting the prognosis of patients, which is similar to the previous results.[21,28]

In summary, MST1/2 and YAP1 should be regarded as effective biomarkers of TNBC. The abnormal expression of MST1/2 and YAP1 might mediate the imbalance of the Hippo signaling pathway, which leads to tumor recurrence and metastasis. In the follow-up study, we will further analyze the mechanism underlying MST1/2 and YAP1 regulating the Hippo signaling pathway in TNBC based on cytological and molecular biological aspects.

Author contributions

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Funding acquisition: Hongfei Ci.
Investigation: Hongfei Ci.
Resources: Qiong Wu.
Software: Hongfei Ci.
Writing – original draft: Yang Feng.
Writing – review & editing: Yang Feng.

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