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MASTL is a potential poor prognostic indicator in ER+ breast cancer

B.-Z. ZHUGE[1], B.-R. DU[2], X.-L. MENG[3], Y.-Q. ZHANG[4]

[1]Clinical Laboratory, Linyi People's Hospital, Linyi, Shandong, China
[2]Department of Anorectal Surgery, Zoucheng People's Hospital, Zoucheng, Shandong, China
[3]1st Department of General Surgery, Linqu People's Hospital, Weifang, Shandong, China
[4]Department of Breast Surgery, Weifang People's Hospital, Weifang, Shandong, China

BaoZhong Zhuge and Bo-Rong Du contributed equally to this study

Abstract. – OBJECTIVE: In this study, we aimed to explore prognostic value of MASTL (microtubule-associated serine/threonine kinase-like) in breast cancer patients on the basis of ER status and molecular subtypes.

MATERIALS AND METHODS: The raw microarray data (GDS5666) of 4T1 derived bone-aggressive explant and primary tumor explant were reanalyzed to identify the dysregulated genes. To pool previous annotated genomic data that assessed the association between MASTL expression and metastatic relapse (MR) risk, MR-free survival, any event (AE, defined as any relapse or death) risk, and AE-free survival in breast cancer patients, a meta-analysis was performed by bc-GenExMiner 4.0.

RESULTS: MASTL is a significantly upregulated gene in 4T1 bone-aggressive explant compared to primary tumor explant. Univariate Cox analysis showed that high MASTL expression is associated with a higher risk of MR (HR: 1.43, 95%CI: 1.28-1.60; $p<0.001$) and a higher risk of AE (HR: 1.27, 95%CI: 1.18-1.37; $p<0.001$) in ER+ breast cancer. Also, high MASTL expression also predicts a worse MR-free survival (HR: 1.74, 95%CI: 1.40-2.17; $p<0.001$) and a worse AE-free survival (HR: 1.42, 95%CI: 1.23-1.63; $p<0.001$) in ER+ breast cancer. However, the associations were not observed in ER- patients. The following NPI adjusted analyses confirmed the results of univariate Cox analysis. In Single Sample Predictors (SSPs) and Subtype Clustering Models (SCMs) subtypes, high MASTL expression is associated with increased risk of AE and predicts a poor AE-free survival in ER+ subgroups.

CONCLUSIONS: MASTL might be a valuable indicator of MR risk and AE risk in ER+ patients, but not in ER- patients.

Key Words:
MASTL, Breast cancer, Metastatic relapse, Any event.

Introduction

Metastasis is one of the most important prognostic factors affecting the survival of breast cancer patients[1,2]. Although the development of early diagnostic tools and therapeutic strategies have a significantly improved prognosis, the development of metastasis is still a major cause of cancer-related death. Currently, the metastatic potential of a primary breast tumor is mainly assessed by pathological characterization of tumor grade and stage[3,4]. Therefore, it is still necessary to investigate the mechanism underlying tumor initiation and progression and to identify reliable biomarkers to predict metastatic likelihood.

One recent study[5] reported that MASTL (microtubule-associated serine/threonine kinase-like) can act as a regulator of the DNA damage response (DDR), a cellular surveillance mechanism, by promoting mitotic progression and cell cycle reentry. Once DNA damage happens, a series of DDR processes such as DNA repair, cell cycle checkpoint, and cell death are immediately initiated[6]. Therefore, it is generally accepted DDR plays a critical role in cancer initiation, progression, and therapy response.

MASTL is upregulated in some types of cancer, including breast cancer[7]. It acts as an oncoprotein that promotes hyperactivation of oncogenic kinase AKT via degradation of its phosphatase, PHLPP, in human malignancies[8]. Its upregulation can enhance cell proliferation under DNA damage stress in squamous cell carcinoma (SCC) cells[7]. Knockdown of MASTL potentiates SCC cells and cervical cancer Hela cells to chemotherapy[7,9]. In breast cancer, MASTL upregulation is correlated with a more advanced clinical stage[7]. However, the prognostic value of MASTL

Corresponding Author: Yong-Qing Zhang, MD; e-mail: yqz80@outlook.com

in breast cancer is still not clear. In this study, by data mining in bc-GenExMiner 4.0, a database of published annotated genomic data including 5609 breast cancer patients[10,11], we assessed the prognostic value of MASTL in breast cancer patients on the basis of the ER status and molecular subtypes.

Materials and Methods

Microarray Reanalysis

The raw microarray data (GDS5666)[12] that compared gene expression profiles among the parental mammary tumor cell line 4T1 and 4T1 derived metastatic populations isolated from liver, lung or bone were downloaded from GEO datasets. The raw data of bone-aggressive explant and primary tumor explant were reanalyzed to identify the dysregulated genes.

Bioinformatic Analysis of the Association between MASTL Expression and Patient Survival

To pool previous annotated genomic data that assessed the association between MASTL expression and metastatic relapse (MR) risk, MR-free survival, any event (AE, defined as any relapse or death) risk and AE-free survival in breast cancer patients, meta-analysis was performed by using bc-GenExMiner 4.0, which is a database of published annotated genomic data including 5609 breast cancer patients[10,11]. Subgroup analysis was performed according to the ER status, or on the basis of molecular subtypes, by Single Sample Predictors (SSPs) or Subtype Clustering Models (SCMs) subtyping method respectively. The prognostic impact of MASTL is evaluated using univariate Cox proportional hazards model, and a forest plot and Kaplan-Meier curves (for the median-split pool). To evaluate the independent prognostic impact of MASTL relative to the Nottingham prognostic index (NPI), a well-established breast cancer prognostic index[13,14], NPI adjusted analysis was further performed.

Results

MASTL is Upregulated in 4T1 Bone-aggressive Explant Compared to Primary Tumor Explant

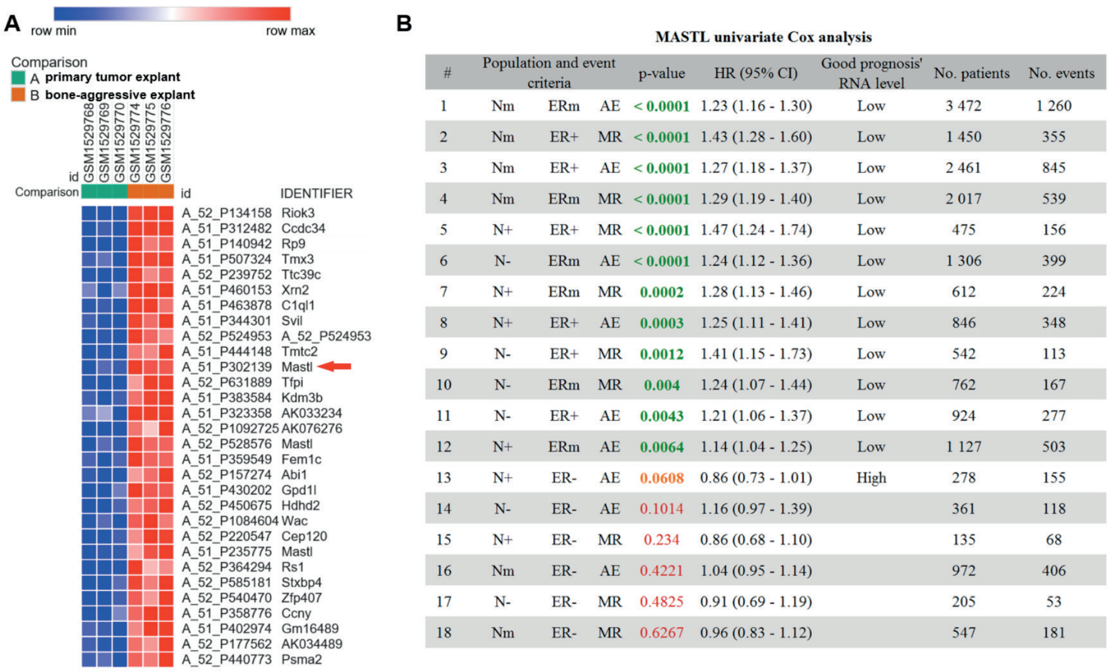
By reanalysis of the raw data of GDS5666, we found that MASTL is a significantly upregulated gene in 4T1 bone-aggressive explant compared to primary tumor explant (Figure 1A, red arrow). Then, we examined whether MASTL upregulation is associated with the risk of poor prognosis in breast cancer, including MR risk and AE risk. By data mining in bc-GenExMiner 4.0, we found 21 studies including 3,472 patients reported the association between MASTL expression and MR or AE (Table I). Then, we performed a preliminary study to explore prognostic analysis for MASTL with any nodal status, any ER status, and any event. The results showed that the in patients with ER+ tumor, low MASTL RNA expression is associated with increased risk of MR and AE (Figure 1B). However, the association was not observed in patients with ER- tumor (Figure 1B). In contrast, high MASTL expression might be associated with decreased risk of AE in patients with nodal negative and ER- tumor at the margin of significance (HR: 0.86, 95%CI: 0.73-1.01, p=0.06) (Figure 1B). These findings suggest that MASTL may have different prognostic value in different subtypes of breast cancer.

MASTL Univariate Cox Analysis and NPI Adjusted Analysis of MR by ER Status

To examine whether MASTL has different prognostic values in ER+ or ER- breast cancer patients, we further performed subgroup analysis. Data analysis showed that 11 studies including 1450 patients assessed the association between MASTL expression and MR risk in ER+ patients (Figure 2A, left). The univariate Cox analysis showed that high MASTL expression is associated with a higher risk of MR (HR: 1.43, 95%CI: 1.28 - 1.60; p<0.001) (Figure 2A, left) and also associated with a worse MR-free survival (HR: 1.74, 95%CI: 1.40-2.17; p<0.001) (Figure 2A, right). NPI adjusted analysis confirmed that high MASTL expression is significantly associated with a higher risk of MR in ER+ patients (HR: 1.23, 95%CI: 1.02-1.49; p=0.034) (Figure 2B). Then, we assessed the association in ER- patients. 11 studies including 547 patients assessed the association between MASTL expression and MR risk in ER- patients (Figure 2C, left). The pooled results indicate no significant association no matter in univariate Cox analysis (Figure 2C) or in NPI adjusted analysis (Figure 2D).

MASTL Univariate Cox Analysis and NPI Adjusted Analysis of AE by ER Status

Then, we examined the prognostic impact of MASTL on AE among the patients with different ER status. 20 studies including 2461 patients assessed the association between MASTL expres-



MASTL univariate Cox analysis

#	Population and event criteria			p-value	HR (95% CI)	Good prognosis' RNA level	No. patients	No. events
1	Nm	ERm	AE	< 0.0001	1.23 (1.16 - 1.30)	Low	3 472	1 260
2	Nm	ER+	MR	< 0.0001	1.43 (1.28 - 1.60)	Low	1 450	355
3	Nm	ER+	AE	< 0.0001	1.27 (1.18 - 1.37)	Low	2 461	845
4	Nm	ERm	MR	< 0.0001	1.29 (1.19 - 1.40)	Low	2 017	539
5	N+	ER+	MR	< 0.0001	1.47 (1.24 - 1.74)	Low	475	156
6	N-	ERm	AE	< 0.0001	1.24 (1.12 - 1.36)	Low	1 306	399
7	N+	ERm	MR	0.0002	1.28 (1.13 - 1.46)	Low	612	224
8	N+	ER+	AE	0.0003	1.25 (1.11 - 1.41)	Low	846	348
9	N-	ER+	MR	0.0012	1.41 (1.15 - 1.73)	Low	542	113
10	N-	ERm	MR	0.004	1.24 (1.07 - 1.44)	Low	762	167
11	N-	ER+	AE	0.0043	1.21 (1.06 - 1.37)	Low	924	277
12	N+	ERm	AE	0.0064	1.14 (1.04 - 1.25)	Low	1 127	503
13	N+	ER-	AE	0.0608	0.86 (0.73 - 1.01)	High	278	155
14	N-	ER-	AE	0.1014	1.16 (0.97 - 1.39)		361	118
15	N+	ER-	MR	0.234	0.86 (0.68 - 1.10)		135	68
16	Nm	ER-	AE	0.4221	1.04 (0.95 - 1.14)		972	406
17	N-	ER-	MR	0.4825	0.91 (0.69 - 1.19)		205	53
18	Nm	ER-	MR	0.6267	0.96 (0.83 - 1.12)		547	181

Figure 1. MASTL is upregulated in 4T1 bone-aggressive explant compared to primary tumor explant. **A.** Heat map of the 30 most upregulated genes in 4T1-derived bone-aggressive cell populations compared to the cells from primary tumor explant. Red: up-regulation. Blue: down-regulation. Image was obtained by re-analysis of the raw microarray data of GDS5666. **B.** Exhaustive MASTL univariate Cox analysis of AE and MR in breast cancer patients. 95% CI: 95% confidence interval; AE: any event; ER (+,-,m): oestrogen receptor status (+: positive, -: negative, m: mixed); HR: hazard ratio; MR: metastatic relapse; N (+,-,m): nodal status (+: positive, -: negative, m: mixed); No. events: number of events; No. patients: number of patients. Data mining was performed in n bc-GenExMiner 4.0.

sion and AR risk in ER+ patients (Figure 3A, left). The univariate Cox analysis showed high MASTL expression is associated with a higher risk of AE (HR: 1.27, 95%CI: 1.18-1.37; $p<0.001$) (Figure 3A, left) and also associated with a worse AE-free survival (HR: 1.42, 95%CI: 1.23-1.63; $p<0.001$) (Figure 3A, right). However, NPI adjusted analysis did not confirm the association (HR: 1.09, 95%CI: 0.95-1.25; $p=0.199$) (Figure 3B). Therefore, we further performed subgroup analysis to explore the causes. By NPI adjusted analysis in N+/ER+ and N-/ER+ patients respectively, we observed the impact of MASTL on AE risk in the N+ subgroup (HR: 1.34, 95%CI: 1.05-1.72; $p=0.019$), but not in the N- subgroup (Figure 3C). As to the association in ER- patients, 18 studies including 972 patients assessed the impact of MASTL expression on MR risk (Figure 3D, left). The pooled results indicate no significant association in univariate Cox analysis (Figure 3D, right). But in NPI adjusted analysis, high MASTL expression might indicate a higher risk of AE at the margin of significance (HR: 1.2, 95%CI: 0.99-1.44; $p=0.06$) (Figure 3E).

MASTL Univariate Cox Analysis of AE by SSP Molecular Subtype

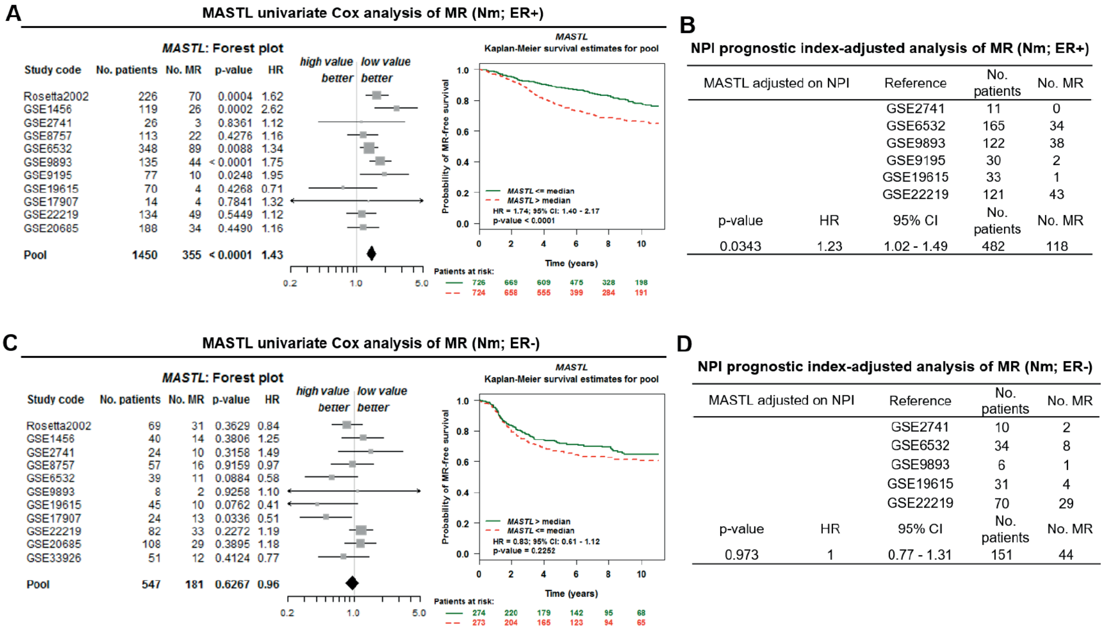
Then, we assessed the prognostic value of MASTL in breast cancer patients in different molecular subtypes. By using the SSP classification, we found that high MASTL expression is associated with increased risk of AE in Luminal A (HR: 1.27, 95%CI: 1.07-1.51; $p=0.006$) and Luminal B breast cancer (HR: 1.23, 95%CI: 1.03-1.46; $p=0.020$) (Figure 4A). In addition, MASTL also predicts poor AE-free survival in Luminal A (HR: 1.40, 95%CI: 1.08-1.81; $p=0.012$) (Figure 4E) and in Luminal B breast cancer (HR: 1.38, 95%CI: 1.01-1.90; $p=0.045$) (Figure 4F). However, no association was observed in other subtypes, including basal-like, HER2+ and normal basal-like (Figure 4A and B-D).

MASTL Univariate Cox Analysis of AE by SCM Molecular Subtype

To examine the robustness of the findings based on SSP molecular subtype, we further performed MASTL univariate Cox analysis by SCM molecular subtype. Consistent with the SSP molecular

Table I. The basic characteristics of studies included.

	Original data		Filtered data	Final data
Study code	**Reference**	**No. patients**	**(any N-ER and AE)**	**No. patients**
Rosetta 2002	Van de Vijver et al, 2002	295	295	295
GSE1378	Ma et al, 2004	59	59	59
GSE1456	Pawitan et al, 2005	159	159	159
GSE2741	Weigelt et al, 2005	50	50	50
GSE4922	Ivshina et al, 2006	249	249	249
GSE8757	Chin et al, 2007	171	171	171
GSE6532	Loi et al, 2007	401	393	393
E_UCON_1	Naderi et al, 2007	135	135	135
GSE9893	Chanrion et al, 2008	155	155	155
GSE9195	Loi et al, 2008	77	77	77
GSE10510	Calabrò et al, 2009	139	134	134
GSE16391	Desmedt et al, 2009	55	55	55
GSE22133	Jönsson et al, 2010	346	339	339
GSE19615	Li et al, 2010	115	115	115
GSE17907	Sircoulomb et al, 2010	55	39	39
GSE22219	Buffa et al, 2011	216	216	216
GSE20711	Dedeurwaerder et al, 2011	85	85	85
GSE20685	Kao et al, 2011	296	296	296
GSE21653	Sabatier et al, 2011	266	252	252
GSE16987	Wang et al, 2011	149	147	147
GSE33926	Kuo et al, 2012	51	51	51
Total	21	5 861	5 790	3 472



A MASTL univariate Cox analysis of MR (Nm; ER+)

MASTL: Forest plot

Study code	No. patients	No. MR	p-value	HR
Rosetta2002	226	70	0.0004	1.62
GSE1456	119	26	0.0002	2.62
GSE2741	26	3	0.8361	1.12
GSE8757	113	22	0.4276	1.16
GSE6532	348	89	0.0088	1.34
GSE9893	135	44	< 0.0001	1.75
GSE9195	77	10	0.0248	1.95
GSE19615	70	4	0.4268	0.71
GSE17907	14	4	0.7841	1.32
GSE22219	134	49	0.5449	1.12
GSE20685	188	34	0.4490	1.16
Pool	**1450**	**355**	**< 0.0001**	**1.43**

B NPI prognostic index-adjusted analysis of MR (Nm; ER+)

MASTL adjusted on NPI	Reference	No. patients	No. MR
	GSE2741	11	0
	GSE6532	165	34
	GSE9893	122	38
	GSE9195	30	2
	GSE19615	33	1
	GSE22219	121	43

p-value	HR	95% CI	No. patients	No. MR
0.0343	1.23	1.02 - 1.49	482	118

C MASTL univariate Cox analysis of MR (Nm; ER-)

MASTL: Forest plot

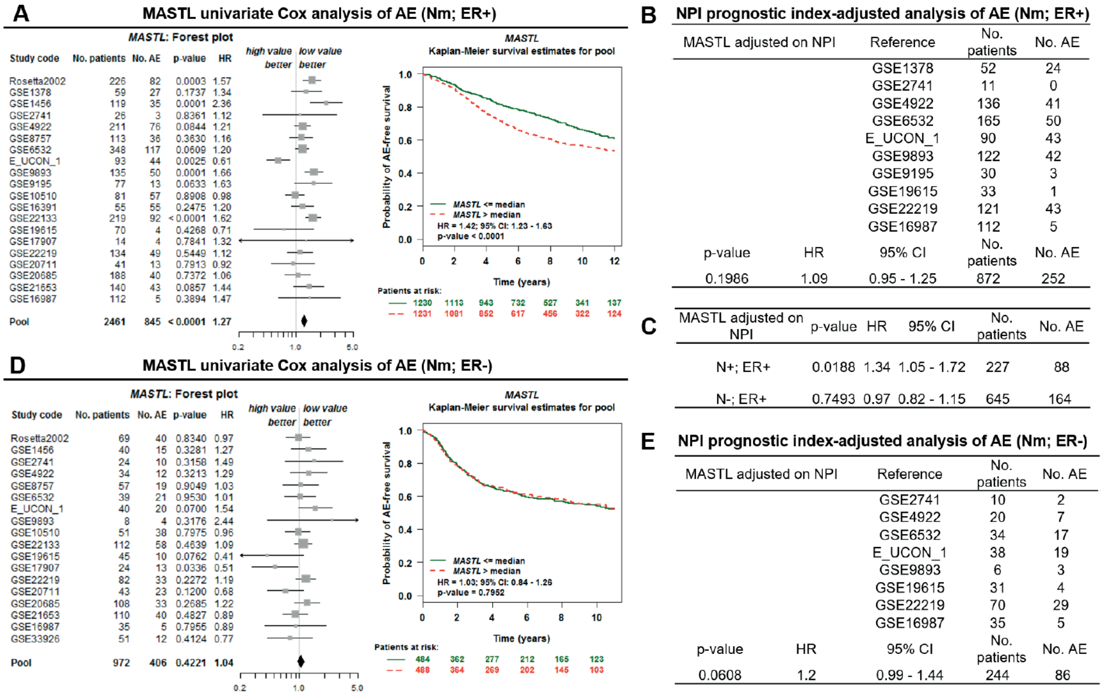
Study code	No. patients	No. MR	p-value	HR
Rosetta2002	69	31	0.3629	0.84
GSE1456	40	14	0.3806	1.25
GSE2741	24	10	0.3158	1.49
GSE8757	57	16	0.9159	0.97
GSE6532	39	11	0.0884	0.58
GSE9893	8	2	0.9258	1.10
GSE19615	45	10	0.0762	0.41
GSE17907	24	13	0.0336	0.51
GSE22219	82	33	0.2272	1.19
GSE20685	108	29	0.3895	1.18
GSE33926	51	12	0.4124	0.77
Pool	**547**	**181**	**0.6267**	**0.96**

D NPI prognostic index-adjusted analysis of MR (Nm; ER-)

MASTL adjusted on NPI	Reference	No. patients	No. MR
	GSE2741	10	2
	GSE6532	34	8
	GSE9893	6	1
	GSE19615	31	4
	GSE22219	70	29

p-value	HR	95% CI	No. patients	No. MR
0.973	1	0.77 - 1.31	151	44

Figure 2. MASTL univariate Cox analysis and NPI adjusted analysis of MR by ER status. ***A and C.*** Forest plots displaying univariate Cox's analysis of MASTL expression and the risk of MR (left) and MR-free survival (right) in ER+ (A) and ER- (C) breast cancer patients. ***B and D.*** NPI adjusted analysis of the association between MASTL expression and the risk of MR in ER+ patients (B) and ER- patients (D). Nm: nodal status mixed. Data mining was performed in bc-GenExMiner 4.0.



A MASTL univariate Cox analysis of AE (Nm; ER+)

MASTL: Forest plot

Study code	No. patients	No. AE	p-value	HR
Rosetta2002	226	82	0.0003	1.57
GSE1378	59	27	0.1737	1.34
GSE1456	119	35	0.0001	2.36
GSE2741	26	3	0.8361	1.12
GSE4922	211	76	0.0844	1.21
GSE8757	113	36	0.3630	1.16
GSE6532	348	117	0.0609	1.20
E_UCON_1	93	44	0.0025	0.61
GSE9893	135	50	0.0001	1.66
GSE9195	77	13	0.0633	1.63
GSE10510	81	57	0.8908	0.98
GSE16391	55	55	0.2475	1.20
GSE22133	219	92	< 0.0001	1.62
GSE19615	70	4	0.4268	0.71
GSE17907	14	4	0.7841	1.32
GSE22219	134	49	0.5449	1.12
GSE20711	41	13	0.7913	0.92
GSE20685	188	40	0.7372	1.06
GSE21653	140	43	0.0857	1.44
GSE16987	112	5	0.3894	1.47
Pool	**2461**	**845**	**< 0.0001**	**1.27**

B NPI prognostic index-adjusted analysis of AE (Nm; ER+)

MASTL adjusted on NPI	Reference	No. patients	No. AE
	GSE1378	52	24
	GSE2741	11	0
	GSE4922	136	41
	GSE6532	165	50
	E_UCON_1	90	43
	GSE9893	122	42
	GSE9195	30	3
	GSE19615	33	1
	GSE22219	121	43
	GSE16987	112	5

p-value	HR	95% CI	No. patients	No. AE
0.1986	1.09	0.95 - 1.25	872	252

C

MASTL adjusted on NPI	p-value	HR	95% CI	No. patients	No. AE
N+; ER+	0.0188	1.34	1.05 - 1.72	227	88
N-; ER+	0.7493	0.97	0.82 - 1.15	645	164

D MASTL univariate Cox analysis of AE (Nm; ER-)

MASTL: Forest plot

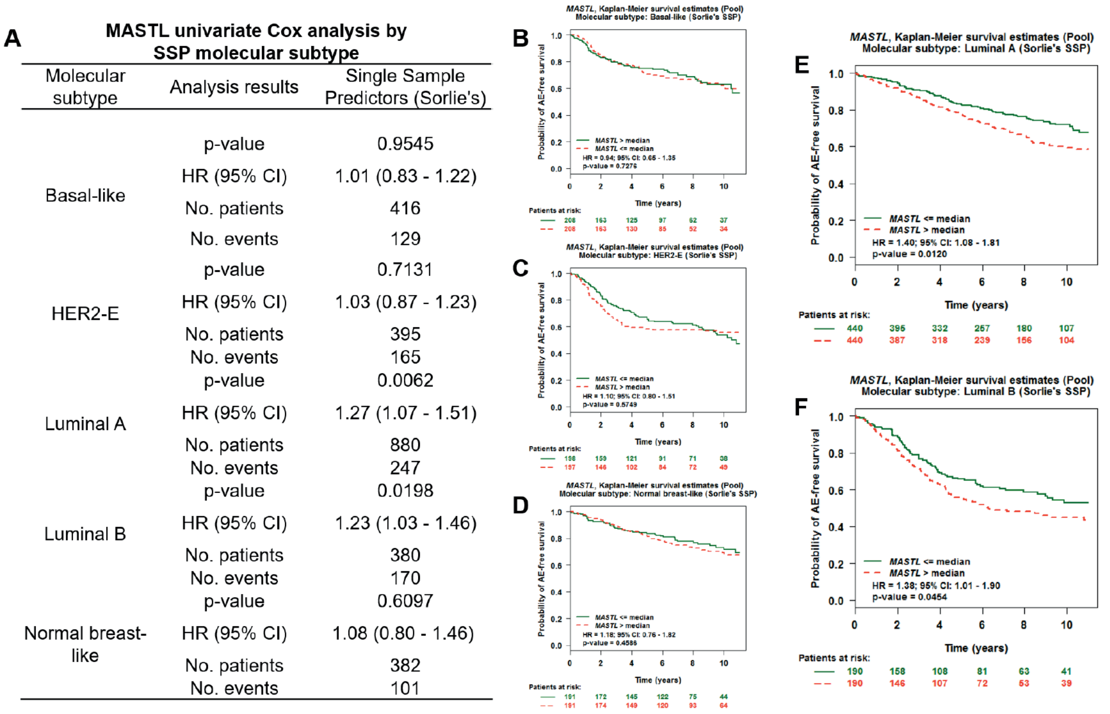
Study code	No. patients	No. AE	p-value	HR
Rosetta2002	69	40	0.8340	0.97
GSE1456	40	15	0.3281	1.27
GSE2741	24	10	0.3158	1.49
GSE4922	34	12	0.3213	1.29
GSE8757	57	19	0.9049	1.03
GSE6532	39	21	0.9530	1.01
E_UCON_1	40	20	0.0700	1.54
GSE9893	8	4	0.3176	2.44
GSE10510	51	38	0.7975	0.96
GSE22133	112	58	0.4639	1.09
GSE19615	45	10	0.0762	0.41
GSE17907	24	13	0.0336	0.51
GSE22219	82	33	0.2272	1.19
GSE20711	43	23	0.1200	0.68
GSE20685	108	33	0.2685	1.22
GSE21653	110	40	0.4827	0.89
GSE16987	35	5	0.7955	0.89
GSE33926	51	12	0.4124	0.77
Pool	**972**	**406**	**0.4221**	**1.04**

E NPI prognostic index-adjusted analysis of AE (Nm; ER-)

MASTL adjusted on NPI	Reference	No. patients	No. AE
	GSE2741	10	2
	GSE4922	20	7
	GSE6532	34	17
	E_UCON_1	38	19
	GSE9893	6	3
	GSE19615	31	4
	GSE22219	70	29
	GSE16987	35	5

p-value	HR	95% CI	No. patients	No. AE
0.0608	1.2	0.99 - 1.44	244	86

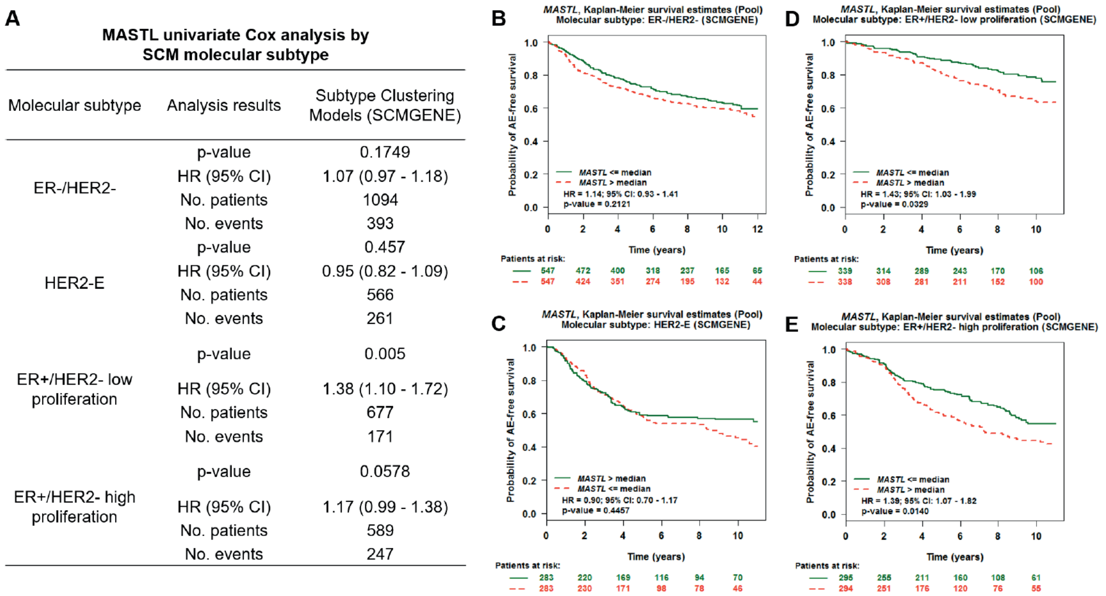
Figure 3. MASTL univariate Cox analysis and NPI adjusted analysis of AE by ER status. ***A and D.*** Forest plots displaying univariate Cox's analysis of MASTL expression and the risk of AE (left) and AE-free survival (right) in ER+ (A) and ER- (D) breast cancer patients. ***B, C and E.*** NPI adjusted analysis of the association between MASTL expression and the risk of MR in ER+ patients (B and C) and ER- patients (E). In ER+ patients, subgroup analysis was performed according to nodal status (C). Nm: nodal status mixed. Data mining was performed in n bc-GenExMiner 4.0.



MASTL univariate Cox analysis by SSP molecular subtype

Molecular subtype	Analysis results	Single Sample Predictors (Sorlie's)
Basal-like	p-value	0.9545
	HR (95% CI)	1.01 (0.83 - 1.22)
	No. patients	416
	No. events	129
HER2-E	p-value	0.7131
	HR (95% CI)	1.03 (0.87 - 1.23)
	No. patients	395
	No. events	165
Luminal A	p-value	0.0062
	HR (95% CI)	1.27 (1.07 - 1.51)
	No. patients	880
	No. events	247
Luminal B	p-value	0.0198
	HR (95% CI)	1.23 (1.03 - 1.46)
	No. patients	380
	No. events	170
Normal breast-like	p-value	0.6097
	HR (95% CI)	1.08 (0.80 - 1.46)
	No. patients	382
	No. events	101

Figure 4. MASTL univariate Cox analysis of AE by SSP molecular subtype (Sorlie's). Univariate Cox's analysis of MASTL expression and the risk of AE ***(A)*** and AE-free survival ***(B-F)*** in breast cancer patients grouped by SSP molecular subtypes (Sorlie's).



MASTL univariate Cox analysis by SCM molecular subtype

Molecular subtype	Analysis results	Subtype Clustering Models (SCMGENE)
ER-/HER2-	p-value	0.1749
	HR (95% CI)	1.07 (0.97 - 1.18)
	No. patients	1094
	No. events	393
HER2-E	p-value	0.457
	HR (95% CI)	0.95 (0.82 - 1.09)
	No. patients	566
	No. events	261
ER+/HER2- low proliferation	p-value	0.005
	HR (95% CI)	1.38 (1.10 - 1.72)
	No. patients	677
	No. events	171
ER+/HER2- high proliferation	p-value	0.0578
	HR (95% CI)	1.17 (0.99 - 1.38)
	No. patients	589
	No. events	247

Figure 5. MASTL univariate Cox analysis of AE by SCM molecular subtype. Univariate Cox's analysis of MASTL expression and the risk of AE ***(A)*** and AE-free survival ***(B-E)*** in breast cancer patients grouped by SCM molecular subtype.

subtype, high MASTL expression is significantly associated with increased risk in ER+/HER2- low proliferation group (HR: 1.38, 95%CI: 1.10-1.72, *p*=0.005) and in ER+/HER2- high proliferation group at the margin of significance (HR: 1.17, 95%CI: 0.99-1.38, *p*=0.058) (Figure 5A). The following Kaplan-Meier Plots showed that high MASTL expression predicts significantly worse

AE-free survivals in ER+/HER2- low proliferation group (HR: 1.43, 95%CI: 1.03-1.99, *p*=0.033) (Figure 5D) and in ER+/HER2- high proliferation group (HR: 1.39, 95%CI: 1.07-1.82, *p*=0.014) (Figure 5E), but not in ER-/HER2- or HER2+ group (Figure 5B-C).

Discussion

MASTL plays an important role in mitotic progression[15]. In brief, MASTL phosphorylates its substratesα-endosulfine (ENSA) and/or cAMP-regulated phosphoprotein 19 (ARPP19). Once phosphorylated, ENSA and ARPP19 inactivate the protein phosphatase 2A complex (PP2A/B55)[15]. PP2A/B55 is the principal protein phosphatase complex that dephosphorylates CDK substrates, including CDK1[15,16]. Therefore, the negative regulative effect of MASTL on PP2A/B55 forms a positive feedback loop that boosts CDK1 activity above the threshold required for mitotic entry[9]. These findings suggest that MASTL is a critical protein modulating cell cycle progression. For the patients with advance breast cancer, therapeutic strategy still largely relies on chemotherapeutic drugs and radiation, using DNA damaging agents. Therefore, MASTL upregulation might be a critical mechanism enhancing the resistance of the cancer cells to treatment and increasing the risk of tumor recurrence and patient mortality.

One recent study[7] reported that MASTL upregulation in breast cancer patients correlated strongly with poor patient survival. However, breast cancer is a clinically heterogeneous disease. The clinical variables including tumor size, lymph-node status, tumor grade, histological type, estrogen receptor (ER) and HER2 receptor status, all influence prognosis and response to systemic therapies[17]. Therefore, it is meaningful to further investigate the prognostic value of MASTL in different subgroups of breast cancer.

In this study, by reanalysis of the raw data of GDS5666, we found that MASTL is a significantly upregulated gene in 4T1 bone-aggressive explant compared to primary tumor explant, suggesting its potential involvement in tumor metastasis. Then, by data mining in bc-GenExMiner 4.0 using univariate Cox analysis, we observed that high MASTL expression is associated with a higher risk of MR (HR: 1.43, 95%CI: 1.28-1.60; *p*<0.001) and a higher risk of AE (HR: 1.27, 95%CI: 1.18-1.37; *p*<0.001) in ER+ breast cancer. Moreover, high MASTL expression also predicts a worse MR-free survival (HR: 1.74, 95%CI: 1.40-2.17; *p*<0.001) and a worse AE-free survival (HR: 1.42, 95%CI: 1.23-1.63; *p*<0.001) in ER+ breast cancer. However, the associations were not observed in ER- patients. The following NPI adjusted analyses also confirmed the results of univariate Cox analysis.

Then, we further assessed the prognostic value of MASTL in different SSP molecular subtypes and different SCM molecular subtypes. According to the SSP classification, we found that high MASTL expression is associated with an increased risk of AE in both Luminal A and Luminal B breast cancer. MASTL also predicts poor AE-free survival in these two subtypes. On the basis of the SCM molecular subtypes, high MASTL expression is significantly associated with increased risk in ER+/HER2- low proliferation group and in ER+/HER2- high proliferation group at the margin of significance. The following Kaplan-Meier Plots showed that high MASTL expression predicts a significantly worse AE-free survival in both ER+/HER2- low proliferation group ER+/HER2- high proliferation group. These results suggest that high MASTL might be a valuable indicator of MR risk and AE risk in ER+ patients, but not in ER- patients.

Conclusions

MASTL might be a valuable indicator of MR risk and AE risk in ER+ patients, but not in ER- patients.

Conflict of interest

The authors declare no conflicts of interest.

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