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Report

Relationship of transgelin expression with clinicopathological characteristics and disease-free survival in HER2-positive breast cancer

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ABSTRACT

Background: Cancer-associated fibroblasts (CAFs) are essential for shaping the tumor microenvironment and influencing therapeutic responses in breast cancer. Thus, a better understanding of the expression of transgelin, a key marker of CAFs, may provide prognostic information. However, the prognostic significance of transgelin in human epidermal growth factor receptor 2 (HER2)-positive breast cancer remains unclear. Here, we investigated the relationship of transgelin expression with clinicopathological characteristics and survival outcomes in HER2-positive breast cancer. **Methods**: Data were collected retrospectively from 111 HER2-positive breast cancer tissue samples. The density of tumor-infiltrating lymphocytes (TILs) was evaluated by hematoxylin and eosin staining. Immunohistochemical staining of transgelin and CD8 was conducted. **Results**: Strong transgelin expression in CAFs was negatively associated with CD8 and TILs ($p < 0.005$). In the multivariate analysis, transgelin expression in CAFs ($p = 0.023$) and pathological stage ($p = 0.029$) were identified as independent prognostic factors for disease-free survival (DFS). The model combining transgelin expression in CAFs and pathological stage improved prediction (−2 log-likelihood = 74.062, Akaike information criterion [AIC] = 78.06) compared with pathological stage alone (−2 log-likelihood = 80.815, AIC = 82.81). Patients in the high-risk group had a shorter DFS ($p < 0.0001$). **Conclusions**: Transgelin expression in CAFs appears to be a novel prognostic marker for HER2-positive breast cancer.

Key words: Disease-free survival, HER2-positive breast cancer, transgelin, CD8

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INTRODUCTION

HER2-positive breast cancer comprises 25% of all breast-cancer cases and is linked to higher recurrence rates and reduced overall survival (OS)[1]. Despite trastuzumab therapy, 15–20 % of HER2-positive breast-cancer patients relapse, highlighting the need for better prognostic markers[1,2].

While traditional treatments have primarily targeted tumor cells (TCs), increasing evidence suggests that the tumor microenvironment (TME) plays a crucial role in cancer progression, therapy resistance, and metastasis. The TME comprises various cellular and non-cellular components, including immune cells, stromal cells, extracellular matrix, and cytokines[3,4]. Among these, CAFs represent the most abundant stromal cells and have been shown to modulate immune responses and promote resistance to therapy in breast cancer[5,6]. Transgelin, a cytoskeletal protein, has been identified as a specific marker for CAFs in several malignancies[6–8].

Due to their important role, CAFs have been the subject of increasing study in recent years[5–11]. However, in Vietnam, research on CAFs—particularly their markers (such as transgelin)—remains limited, highlighting the need for further investigation. This study aims to examine the relationship of transgelin expression with clinicopathological characteristics and survival outcomes in HER2-positive breast cancer.

METHODS

Collection of clinical samples

In total, 111 mastectomy specimens were collected from HER2-positive breast-cancer patients who had received no pre-operative therapy. Patients with invasive lobular carcinoma, mixed invasive ductal and lobular carcinoma, invasive micropapillary carcinoma, mucinous carcinoma, or inadequate tissue blocks (<5 % tumor/stroma) were excluded[12].

Data were abstracted from medical records and included age, tumor size, histology, histologic grade, vascular invasion, lymph-node metastasis, pathological stage, estrogen-receptor (ER) expression, progesterone-receptor (PR) expression, HER2 expression, tumor-cell proliferation index (Ki-67 expression), and treatment regimen.

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Unfavorable outcomes comprised ipsilateral locoregional invasive breast-tumor recurrence, contralateral invasive breast cancer, distant disease recurrence, or death from any cause. Overall-survival (OS) and disease-free-survival (DFS) data were obtained from medical records or by patient contact.

All data were collected at the National Cancer Hospital (Hanoi, Vietnam) between 1 January 2017 and 31 December 2021, with follow-up completed by 31 December 2024.

The study was approved by the Hanoi Medical University Ethics Committee (code: IRB-VN01.001/IRB00003121/FWA 00004148) and was conducted in accordance with the Declaration of Helsinki.

Hematoxylin and eosin staining

The hematoxylin-and-eosin (H&E) staining protocol is provided in **Supplementary S1**.

Histological examination

Whole sections of H&E-stained slides were used to evaluate stromal TILs in strict accordance with the criteria proposed by the International TIL Working Group[13]. The percentage of all mononuclear cells (including lymphocytes and plasma cells) in the stromal compartment within the border of the invasive tumor was assessed visually. TILs were scored in 5 % increments and classified as <50 % or ≥50 %, following Swisher[14].

Immunohistochemical staining

The immunohistochemical (IHC) protocol is provided in **Supplementary S2**.

CD8 assessments

Whole-section slides were scanned with a Leica Aperio AT2 (40×). CD8 expression on the membrane and in the cytoplasm was analyzed across the entire tumor area using QuPath software[15]. High CD8 expression was defined as ≥10 % CD8-positive lymphocytes among nucleated stromal cells, as described by L. Zong[12].

Transgelin assessments

Transgelin expression in CAFs: nuclear and/or cytoplasmic staining was graded as 0 (no staining), 1 (light brown), 2 (brown), or 3 (dark brown). Grades 0–1 were considered weakly positive, whereas grades 2–3 were considered strongly positive[11].

Transgelin expression in TCs: a result was deemed positive when ≥10 % of tumor cells showed dark-brown cytoplasmic staining[7]. All assessments were performed by two pathologists; discrepancies were resolved by a third pathologist.

Statistical analysis

Data were entered in EpiData 4.6.0.4 (EpiData Association, Denmark) and analyzed in R 4.1.2 (https://www.r-project.org). Associations between transgelin expression and clinicopathological characteristics were examined with the χ^2 test or Fisher's exact test. Survival was analyzed with the Kaplan–Meier method and log-rank test. Variables with $p < 0.05$ in univariate Cox regression and post-hoc power ≥80 % were included in the multivariate model. Model fit was evaluated with −2 log-likelihood and the AIC. Risk groups were compared with the Kaplan–Meier method. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The distribution of clinicopathological characteristics and transgelin expression is shown in **Table 1**. The median patient age was 50 years (range, 29–74 years). Most tumors were invasive ductal carcinomas; three were tubular carcinomas and one was metaplastic carcinoma, not otherwise specified. All patients were treated in accordance with Vietnam's breast-cancer guidelines and underwent surgery. Hormone receptor-positive cases received tamoxifen plus chemotherapy, whereas hormone receptor-negative cases received chemotherapy alone. Regimens consisted of four cycles of AC (doxorubicin/cyclophosphamide) or six cycles of FAC (5-FU/doxorubicin/cyclophosphamide). Fifty-two patients received trastuzumab. In the entire cohort, the median percentages of TILs and $CD8^+$ cells were 17.4% (interquartile range [IQR], 0.0%–80.0%) and 8.9% (IQR, 0.0%–66.7%), respectively (**Figure 1** and **Supplementary Fig.**).

Table 1: **Baseline characteristics of the entire patient cohort (N=111)**

Parameters	N	Percent
Age (years)		
< 50	51	45.9
≥ 50	60	54.1
Tumor size (cm)		
< 2	32	28.8
2-5	79	71.2
Histology		
Ductal carcinoma	107	96.4
Others	4	3.6
Histologic grade		
1 - 2	56	50.5
3	55	49.5
Vascular invasion		
No	73	65.8
Yes	38	34.2
Lymph node metastases		
< 2	92	82.9
≥ 2	19	17.1
Pathological stage		
Early stage (IA, IIA, T2N1)	87	78.4
Locally advanced stage (IIB, T3N0, IIIA-C)	24	21.6
ER expression		
Negative	56	50.5
Positive	55	49.5
PR expression		
Negative	64	57.7
Positive	47	42.3
HER2 expression		
IHC 2+ ISH +	31	27.9
IHC 3+	80	72.1
Ki67 expression		
Low (< 20%)	7	6.3
High (≥ 20%)	104	93.7
Transgelin expression in TCs		
Negative (< 10%)	90	81.1
Positive (≥ 10%)	21	18.9
Transgelin expression in CAFs		
Weak (Grade 0,1)	74	66.7
Strong (Grade 2,3)	37	33.3
CD8 expression		
Low (< 10%)	80	72.1
High (≥ 10%)	31	27.9
TILs		
Low (< 50%)	98	88.3
High (≥ 50%)	13	11.7
Trastuzumab		
No	59	53.2
Yes	52	46.8

Abbreviations: **CAFs**: Cancer-associated fibroblasts, **ER**: Estrogen receptor, **HER2**: Human epidermal growth factor receptor 2, **IHC**: immunohistochemistry, **ISH**: In situ hybridization, **Ki67**: Tumor cell proliferation index, **PR**: Progesterone receptor, **TCs**: Tumor cells, **TILs**: Tumor-infiltrating lymphocytes.

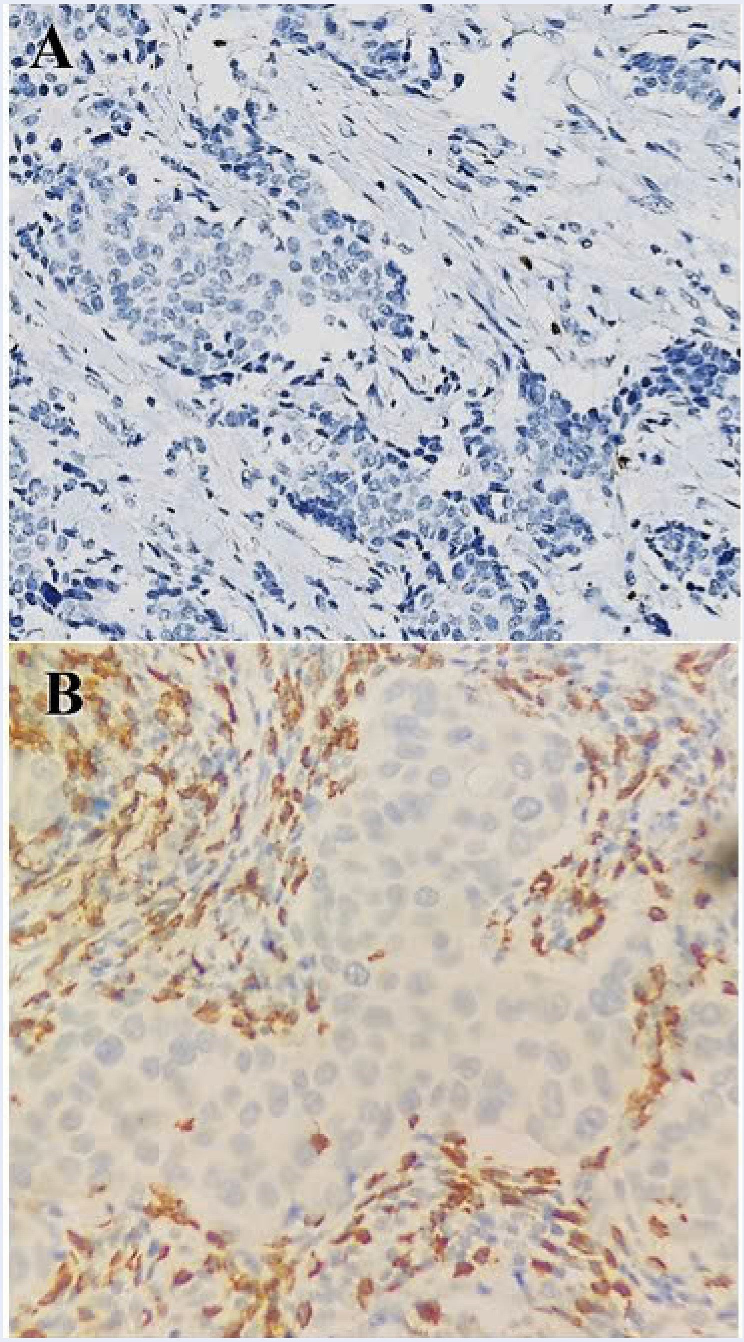

Figure 1: **HER2-positive breast cancer**. Staining CD8 in original magnification 20x: Low (**A**), and high (**B**) expression.

Table 2: Association of transgelin marker with clinicopathologic characteristics (N=111)

Parameters	Transgelin in TCs positive N (%)	P-value	Strong transgelin expression in CAFs N (%)	P-value
<50	9 (17.6)	0.752	17 (33.3)	1.000
≥50	12 (20.0)		20 (33.3)	
Tumor size (cm)				
<2	5 (15.6)	0.573	8 (25.0)	0.236
≥2	16 (20.3)		29 (36.7)	
Histologic grade				
1 - 2	7 (12.5)	0.081	20 (35.7)	0.591
3	14 (25.5)		17 (30.9)	
Vascular invasion				
No	11 (15.1)	0.151	31 (33.7)	0.859
Yes	10 (26.3)		6 (31.6)	
Lymph node metastases				
<2	17 (18.5)	0.755a	14 (15.2)	0.507a
≥2	4 (21.1)		4 (21.1)	
Pathological stage				
Early stage (IA, IIA, T2N1)	13 (14.9)	0.073a	28 (32.3)	0.625
Locally advanced stage (IIB, T3N0, IIIA-C)	8 (33.3)		9 (37.5)	
ER expression				
Negative	16 (28.6)	0.009	19 (33.9)	0.893
Positive	5 (9.1)		18 (32.7)	
PR expression				
Negative	17 (26.6)	0.016	21 (32.8)	0.892
Positive	4 (8.5)		16 (34.0)	
Ki67 expression				
Low (<20 %)	0 (0.0)	0.343a	3 (42.9)	0.864a
High (≥20 %)	21 (20.2)		34 (32.7)	
Transgelin expression in TCs				
Negative (<10 %)			29 (32.2)	0.607
Positive (≥10 %)			8 (38.1)	
Transgelin expression in CAFs				
Weak (Grade 0,1)	13 (17.6)	0.607		
Strong (Grade 2,3)	8 (21.6)			
CD8 expression				
Low (<10%)	13 (16.3)	0.249	36 (45.0)	<0.001a
High (≥10%)	8 (25.8)		1 (3.2)	
TILs				
Low (<50%)	18 (18.4)	0.709a	37 (37.8)	0.004a
High (≥50%)	3 (23.1)		0 (0.0)	

Abbreviations: **CAFs**: Cancer-associated fibroblasts, **ER**: Estrogen receptor, **Ki67**: Tumor cell proliferation index, **PR**: Progesterone receptor, **TCs**: Tumor cells, **TILs**: Tumor-infiltrating lymphocytes. a Fisher's exact test.

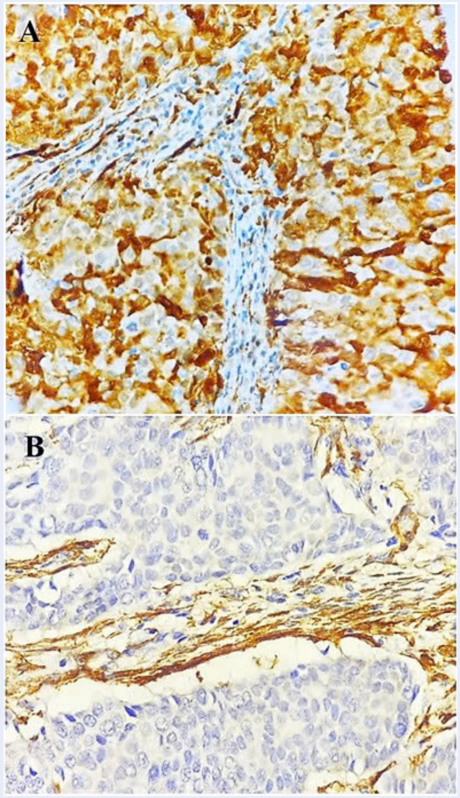

Figure 2: **HER2-positive breast cancer**. Transgelin expression in tumor cells at original magnification 40x: positive (**A**); negative (**B**)

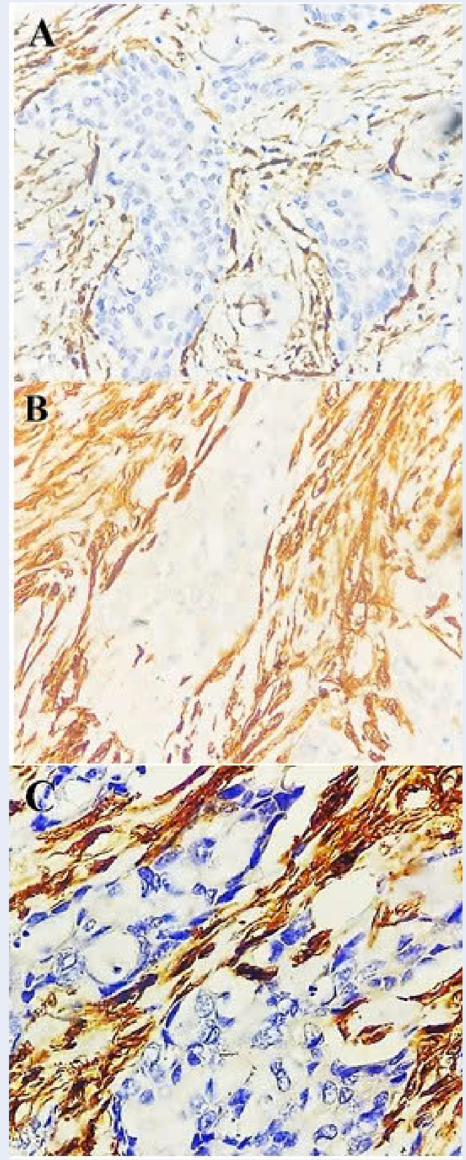

Figure 3: **HER2-positive breast cancer**. Transgelin expression in cancer-associated fibroblasts at original magnification 40x: Grade 1 (**A**), grade 2 (**B**), and grade 3 (**C**) expression. Negative immunostaining for transgelin was not shown here.

Association of transgelin with clinicopathological characteristics

As shown in **Table 2**, strong transgelin expression in CAFs was negatively associated with CD8 expression ($p < 0.001$) and TILs ($p = 0.004$). Transgelin expression in TCs was positively associated with ER status ($p = 0.009$) and PR status ($p = 0.016$) (**Figure 2** and **Figure 3**).

Association of transgelin expression and clinicopathological characteristics with clinical outcomes

The analysis included 81 women with a median follow-up of 65 months (range, 29–96 months). Ten patients (12.3%) experienced recurrence and three (3.7%) died. The 5-year OS and DFS rates were 93% and 84%, respectively. Owing to the low number of deaths, we focused on associations between transgelin expression, clinicopathological characteristics, and DFS. Univariate analysis (**Table 3**) identified two variables associated with shorter DFS: strong transgelin expression in CAFs ($p = 0.030$) and a locally advanced pathological stage ($p = 0.045$). Post-hoc power analysis yielded 98.9% for transgelin expression in CAFs and 88.4% for pathological stage ($\alpha = 0.05$). In multivariate analysis (**Table 3**), transgelin expression in CAFs (hazard ratio [HR] = 6.082; 95% confidence interval [CI], 1.286–28.758; $p = 0.023$) and pathological stage (HR = 4.001; 95% CI, 1.154–13.873; $p = 0.029$) were independent prognostic factors for

Table 3: Association of transgelin and clinicopathological characteristics with disease-free survival in HER2-positive breast cancer (N=81)

Parameters		Log rank	Univariable Cox regression		Multivariate Cox regression	
			HR (95%CI)	p-value	HR (95%CI)	p-value
Age (years)	< 50	0.352	1			
	≥50		1.882 (0.486 – 7.283)	0.360		
Histologic grade	1 - 2	0.708	1			
	3		1.247 (0.359 – 4.518)	0.708		
Vascular invasion	No	0.740	1			
	Yes		1.239 (0.349 - 4.396)	0.740		
Pathological stage	Early stage (IA, IIA, T2N1)	0.032	1		1	
	Locally advanced stage (IIB, T3N0, IIIA-C)		3.561 (1.030 – 12.312)	0.045	4.001 (1.154 – 13.873)	0.029
ER expression	Negative	0.656	1			
	Positive		1.326 (0.382 – 4.606)	0.657		
PR expression	Negative	0.263	1			
	Positive		0.423 (0.090 – 1.997)	0.277		
Ki67 expression	Low (<20 %)	0.506	1			
	High (≥20 %)		0.502 (0.063 – 3.978)	0.514		
Transgelin expression in TCs	Negative (<10 %)	0.543	1			
	Positive (≥10 %)		0.619 (0.131 – 2.935)	0.546		
Transgelin expression in CAFs	Weak (Grade 0,1)	0.014	1		1	
	Strong (Grade 2,3)		5.559 (1.180 – 26.191)	0.030	6.082 (1.286 – 28.758)	0.023
CD8 expression	Low (<10%)	0.165	1			
	High (≥10%)		0.258 (0.033 – 2.033)	0.198		
TILs	Low (<50%)	0.288	1			
	High (≥50%)		0.042 (0.000 – 349.497)	0.492		
Trastuzumab	No	0.955	1			
	Yes		0.965 (0.278 – 3.348)	0.955		

Abbreviations: CAFs: Cancer associated fibroblasts, **CI**: Confidence interval, **ER**: Estrogen receptor, **HER2**: Human epidermal growth factor receptor 2, **HR**: Hazard ratio, **Ki67**: Tumor cell proliferation index, **PR**: Progesterone receptor, **TCs**: Tumor cells, **TILs**: Tumor-infiltrating lymphocytes.

DFS. Adding transgelin expression in CAFs to the pathological-stage model improved model performance, lowering the −2 log-likelihood from 80.815 to 74.062 (p = 0.004) and the AIC from 82.81 to 78.06 (**Table 4**). Patients classified as high-risk (strong transgelin expression in CAFs and a locally advanced pathological stage) had a significantly shorter DFS than the low-risk group (p < 0.0001; **Figure 4**).

DISCUSSION

This study found that strong transgelin expression in CAFs was negatively associated with $CD8^+$ cells and TILs. Transgelin expression in TCs was positively associated with ER and PR status. We confirmed that transgelin expression in CAFs and pathological stage were independent prognostic factors for DFS. Including transgelin expression in CAFs in the predictive model provided additional prognostic information beyond pathological stage alone. All patients received no neoadjuvant therapy; stained sections were obtained from resected tumors, accurately reflecting the TME.

In our study, CD8 expression was positively associated with TILs. However, like Liu (2011)[16], we did not identify a significant association between CD8 expression and improved DFS. This discrepancy may be attributed to variations in CD8 evaluation methods across studies. Whereas our analysis focused on CD8 in the stromal compartment, other studies have assessed intratumoral compartments or both together[17,18], potentially leading to differing prognostic implications. Furthermore, chronic antigen stimulation within the TME can lead to exhaustion of CD8 effector T cells, reducing their antitumor activity[19].

Several studies have investigated the relationship between CAFs and transgelin, a cytoskeletal protein that plays a role in fibroblast activation and tumor progression. Transgelin expression varies between TCs and the surrounding stroma, with significant up-regulation in CAFs compared with TCs. These findings suggest that transgelin is a key marker of fibroblast activation and may contribute to the protumor behavior of CAFs[9,10]. Our study showed that transgelin expression was higher in CAFs than in TCs and was significantly associated with short DFS, similar to findings reported previously[6–8]

In our study, strong transgelin expression in CAFs was negatively associated with CD8 and TILs, consistent with previous research[20,21]. CAFs shape the TME by modulating CD8 responses through antigen presentation and up-regulating immune checkpoints, leading to T-cell impairment and tumor immune evasion[22].

Transgelin expression in TCs was positively associated with ER and PR status, in agreement with earlier studies[23,24]. However, unlike its prognostic value in CAFs, transgelin expression in TCs was not linked to DFS, suggesting different roles in the stromal and tumor compartments.

Although the number of DFS events was limited, we performed a post-hoc power analysis and model comparisons to enhance the reliability of the findings. Both transgelin expression in CAFs and pathological stage demonstrated sufficient power to detect meaningful associations and were confirmed as independent prognostic factors in the multivariate analysis. Their combination improved model performance, as shown by a lower −2 log-likelihood and the lowest AIC among the tested models. Patients in the high-risk group had a shorter DFS than those in the low-risk group.

This study has several limitations. The small number of DFS events may reduce statistical power and affect the stability of the multivariate analysis. The retrospective, single-center design may also limit generalizability. Finally, the wide confidence intervals (particularly for transgelin) suggest uncertainty in the effect estimates.

CONCLUSIONS

Transgelin expression in CAFs may help predict DFS in patients with HER2-positive breast cancer. Further multicenter studies with larger cohorts are needed to validate these results.

ABBREVIATIONS

AIC- Akaike information criterion, **CAFs-** Cancer-associated fibroblasts, **CI-** Confidence interval, **DFS-** Disease-free survival, **ER-** Estrogen receptor, **H&E-** Hematoxylin and eosin, **HER2-** Human epidermal growth factor receptor 2, **HR -** Hazard ratio, **IHC-** Immunohistochemistry, **ISH-** In situ hybridization, **IQR-** Interquartile range, **Ki67-** Tumor cell proliferation index, **OS-** Overall survival, **PR-** Progesterone receptor, **TCs-** Tumor cells, **TILs-** Tumor-infiltrating lymphocytes, **TME-** Tumor microenvironment.

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Author's contributions

NTT, NVH: Conceptualization, methodology, writing-original draft preparation. NVC, LTT:

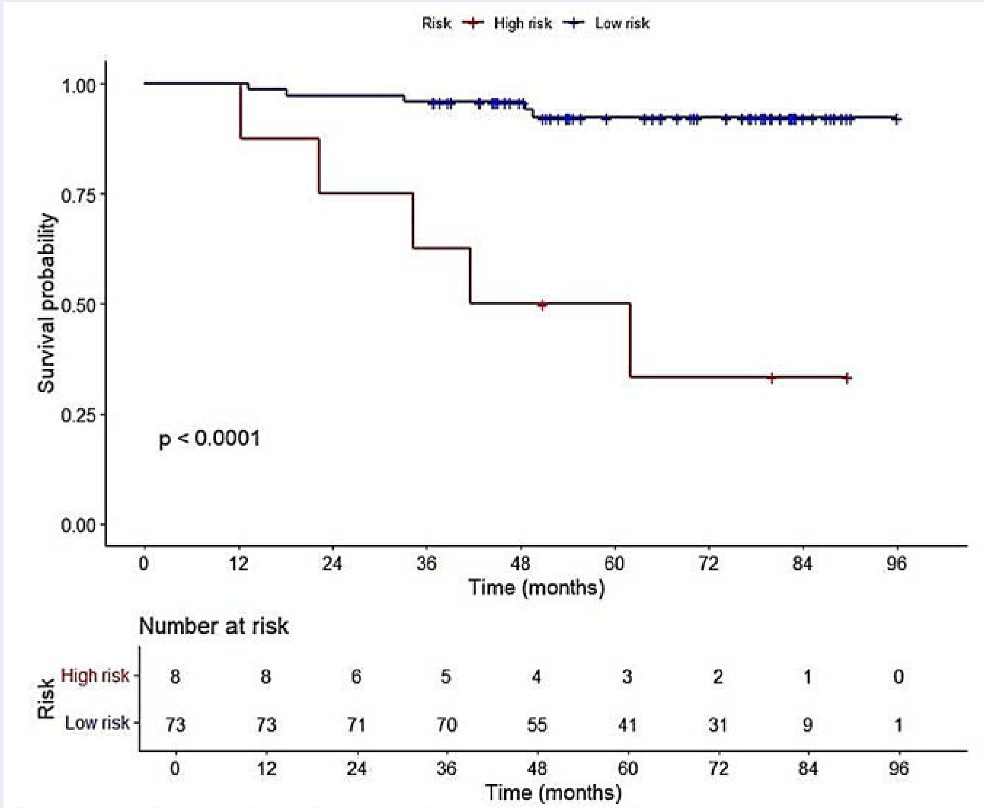

Figure 4: **Risk stratification based on pathological stage and transgelin expression in cancer-associated fibroblasts**. Kaplan–Meier curves were used to assess survival differences between high and low-risk groups. Patients in the high-risk group had shorter disease-free survival compared to those in the low-risk group.

Table 4: **Additional (Disease-free survival) value of transgelin marker to prognostic multivariable models (N=81)**

Model variables	-2 Log Likelihood	Likelihood ratio P value	AIC
Pathological stage	80.815	0.032	82.81
Pathological stage + transgelin expression in CAFs	74.062	0.004	78.06

Abbreviations: **AIC**: Akaike information criterion, **CAFs**: Cancer-associated fibroblasts.

Visualization, methodology. NTT, NVH, LTT: Data curation, writing-original draft preparation. NVC, LPT: Validation, investigation, supervision, and critical revision of the manuscript. All authors read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Hanoi Medical University (IRB-VN01.001/IRB00003121/FWA 00004148) and adhered to the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's mother for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors declare that they have not used generative AI (a type of artificial intelligence technology that can produce various types of content including text, imagery, audio and synthetic data. Examples include ChatGPT, NovelAI, Jasper AI, Rytr AI, DALL-E, *etc.*) and AI-assisted technologies in the writing process before submission.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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