THE PROGNOSTIC SIGNIFICANCE OF TUMOR-INFILTRATING LYMPHOCYTES IN RESECTABLE TRIPLE-NEGATIVE BREAST CANCER—INSIGHTS FROM SEVEN YEARS OF REAL-WORLD DATA

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Abstract

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype with limited treatment options and a high risk of recurrence. Tumor-infiltrating lymphocytes (TILs) are potential prognostic markers of TNBC. While studies in Western populations suggest favorable outcomes with higher TIL levels, evidence from Southeast Asian populations remains limited. Objectives: This study aimed to evaluate the prognostic impact of TIL levels on survival outcomes in patients with resectable TNBC.

Methods: We retrospectively reviewed patients with resectable TNBC who underwent upfront surgery at the Ramathibodi Comprehensive Cancer Center in Thailand between 2015 and 2019. All patients were staged according to the AJCC 8th edition. TILs were assessed using the International TILs Working Group 2014 guidelines. The patients were categorized by TIL levels. The primary endpoint was relapse-free survival (RFS), and patients with TILs ≥30% were compared with those with TILs <30%. Secondary endpoints included RFS with TILs cutoffs (≥ 10% and ≥20%), breast cancer-specific survival (BCSS), and overall survival (OS).

Results: The study included 128 patients with a median follow-up of 83 months. Adjuvant chemotherapy was administered in 84.4% of cases, whereas omission was mainly in older or comorbid patients. Patients with TILs ≥30% showed a favorable but non-significant trend toward improved RFS (HR 0.54; 95% CI, 0.20–1.49; $p = 0.238$), BCSS (HR 0.43; 95% CI, 0.09–1.97), and OS (HR 0.67; 95% CI, 0.22–2.06). Lower TIL thresholds (≥10%, ≥20%) were not associated with improved outcomes. A multivariate analysis showed no independent prognostic effect of TILs.

Conclusion: Although statistical significance was not reached, TIL levels ≥30% were associated with a favorable survival trend. To our knowledge, this is the largest Southeast Asian cohort with long-term follow-up, providing region-specific real-world evidence. These findings illustrate that TIL assessment on routine H&E slides is feasible and practical, especially in resource-constrained settings, and highlight the need for larger prospective studies to clarify the prognostic and predictive role of TILs in the immunotherapy era.

Keywords: triple-negative breast cancer, tumor-infiltrating lymphocytes (TILs), prognosis, relapse-free survival, breast cancer-specific survival, Southeast Asia, Thailand

J Southeast Asian Med Res 2026: 10: e0255
https://doi.org/10.55374/jseamed.v10.255

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Received: 26 September 2025
Revised: 3 March 2026
Accepted: 17 April 2026

Introduction

Breast cancer is the most common cancer among women worldwide, including in Thailand.[1] Breast cancer is classified into four subtypes based on hormone receptor and human epidermal growth factor receptor 2 (HER2) expression as follows: hormone receptor-positive/HER2-negative, hormone receptor-positive/HER2-positive, HER2-enriched, and triple-negative (hormone receptor-negative/HER2-negative).[2] The prognosis of breast cancer depends on several factors, such as age, stage, and molecular subtype. Among these, triple-negative breast cancer (TNBC) accounts for 15–20% of all breast cancers, which is recognized as the most aggressive subtype.[3]

TNBC is a heterogeneous disease that shows greater molecular diversity than other breast cancer subtypes. Several studies have proposed molecular classifications of TNBC, and the current consensus has identified at least four major molecular subtypes: basal-like immune-suppressed (25%–40%), basal-like immune-activated (20%–30%), luminal androgen receptor (15%–25%), and mesenchymal (15%–20%).[4-6] Among these, the immune-related subtypes—particularly the immunomodulatory types—are associated with better chemotherapy responsiveness and more favorable clinical outcomes than other subtypes.[7] This molecular diversity indicates the substantial prognostic heterogeneity observed in TNBC in both the early and advanced stages of the disease.

Tumor-infiltrating lymphocytes (TILs) are immune cells—primarily T cells but also B cells and natural killer cells—that migrate into the tumor microenvironment, reflecting an active anti-tumor immune response. Tumors can be classified according to the following CD8+ T cell infiltration patterns: "immune deserts" lack considerable infiltration, whereas "fully inflamed" tumors show abundant intratumoral CD8+ T cells. In TNBC, the density, composition, and spatial distribution of TILs are associated with prognosis and therapeutic response, particularly to immunotherapy.[8] The International TILs Working Group 2014 provided standardized recommendations for evaluating TILs on hematoxylin and eosin (H&E)-stained slides in breast cancer. The inter-observer agreement for TIL assessment has been specifically examined in the TNBC and HER2-positive subtypes.[9]

TNBC is considered the most immunogenic breast cancer subtype because it typically shows higher levels of TILs compared with other subtypes. TILs are promising biomarkers in early-stage TNBC, with their levels serving as indicators of prognosis and chemotherapy responsiveness.[10-12] A pooled analysis by Loi et al. showed that high stromal TIL levels (≥30%) were associated with improved survival following standard anthracycline-based adjuvant chemotherapy.[13] Similarly, the PARADIGM study assessed TILs in patients with node-negative TNBC from a Dutch population-based registry who did not receive neoadjuvant or adjuvant systemic therapy[14]. This study showed that TIL levels ≥30% were associated with improved disease-free survival (DFS) and overall survival (OS) in patients with stage I. Additionally, a pooled analysis by Denkert et al. showed that higher TIL concentrations predicted a pathological response to neoadjuvant chemotherapy and were associated with improved survival.[15] These findings support the hypothesis that TNBC is highly immunogenic and suggest that TILs have prognostic and predictive value in this disease.

Although TILs are potential prognostic biomarkers in breast cancer, the optimal cutoff values for defining high versus low TIL levels remain controversial, with no clear consensus. Prior studies have used a range of cutoffs, typically between 10% and 50%, depending on study design and clinical context. Notably, a threshold of ≥30% has been commonly used to define "high" TIL levels and has been associated with improved clinical outcomes in several studies, including pooled analyses and population-based cohorts.[13-15] This cutoff is also supported by the International TILs Working Group as a clinically meaningful threshold for risk stratification.[16] Therefore, we selected a 30% cutoff for the primary analysis and explored alternative thresholds (10% and 20%) in secondary analyses.

Furthermore, data on the prognostic value of TILs in Southeast Asian populations are limited. Given potential differences in tumor biology and immune profiles across ethnicities, this study aimed to evaluate TIL levels and their prognostic significance in patients with resectable TNBC in a Southeast Asian population.

Methods

Ethics approval

Approval was granted by the Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. (COA. MURA 2024/441) This study was conducted in accordance with the principles of the Declaration of Helsinki, the Belmont Report, the CIOMS Guidelines, and the International Conference on Harmonization Good Clinical Practice (ICH-GCP). The requirement for informed consent was waived by the committee in accordance with institutional policy and national guidelines for retrospective research involving anonymized data, as outlined by the Ministry of Public Health, Thailand.

Study design

All patients underwent definitive primary surgery prior to receiving any additional treatment. Eligible patients were diagnosed with resectable TNBC, defined as stage I-III disease, between 1 January 2015 and 1 December 2019, and were retrospectively staged according to the American Joint Committee on Cancer 8th edition. Clinicopathological data and survival outcomes were retrospectively collected from the Ramathibodi Cancer Registry, which is a tertiary care and referral hospital in Bangkok, Thailand. H&E-stained slides were reviewed, and stromal TILs were evaluated by experienced pathologists. The patients were categorized based on TIL levels for comparative analysis of clinical outcomes. The last follow-up cutoff date was 31 December 2024.

Inclusion and exclusion criteria

The inclusion criteria were as follows: patients aged 18 years or older with a histologically confirmed diagnosis of invasive breast carcinoma; those who were negative for estrogen and progesterone receptors and HER2-negative (defined as Immunohistochemistry 0–1+ or IHC 2+ with negative Fluorescence In Situ hybridization results), thus meeting the definition of TNBC; and the availability of H&E-stained slides from surgical specimens containing at least 10% invasive → carcinoma. The exclusion criteria included patients who had received neoadjuvant chemotherapy (NCT), had insufficient or missing data (e.g., incomplete pathological/medical records), had unavailability or poor-quality H&E-stained slides, or had specimens obtained via core-needle biopsy.

Treatment characteristics

Treatment information was retrospectively collected from medical records. The majority of patients received adjuvant anthracycline- and/or taxane-based chemotherapy, whereas chemotherapy was omitted in a minority of cases, typically because of advanced age, comorbidities, or patient refusal. Adjuvant radiotherapy was administered at the treating oncologist's discretion.

Study endpoints

The primary endpoint was relapse-free survival (RFS), comparing patients with TILs ≥30% versus those with TILs <30%. Secondary endpoints included RFS stratified by TIL thresh-

olds of ≥20% and ≥10%. Additional secondary endpoints were breast cancer–specific survival (BCSS) and overall survival (OS) among patients with TILs ≥30% versus <30%. Exploratory subgroup analyses were conducted based on receipt of adjuvant chemotherapy. RFS was defined as the time from primary treatment to disease recurrence (local, regional, or distant). BCSS was defined as the time from diagnosis to death specifically attributable to breast cancer.

Pathological analysis

The evaluation of TILs on H&E-stained slides was performed by experienced pathologists blinded to patients' clinical data. The assessment focused on the stromal compartment and was conducted in accordance with the International TILs Working Group 2014 guidelines. [17] An example of evaluating TILs on an H&E-stained slide is shown in **Supplementary Figure S1.**

Statistical analysis

Clinicopathological characteristics are summarized using descriptive statistics. Categorical variables were compared using the chi-square test or Fisher's exact test, while continuous variables were analyzed using Student's t-test. RFS and BCSS were estimated using the Kaplan–Meier method, and differences between groups were evaluated using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards regression model. Univariate and multivariate Cox regression analyses were performed to identify the prognostic factors associated with RFS in patients with resectable TNBC. All statistical analyses were conducted using STATA software, version 16. A p-value <0.05 was considered statistically significant. The sample size was determined by the number of eligible patients during the study period.

Results

Patient selection and clinical characteristics

Among the patients diagnosed with stages I–III breast cancer, 225 with resectable TNBC were identified from the Ramathibodi Cancer Registry. Of these, 57 were excluded because of receiving neoadjuvant chemotherapy (n=24) or a lack of biopsy specimens (n=33). An additional 40 patients were excluded because of unavailable or inadequate tissue blocks. The remaining 128 patients were included in the analysis (**Figure 1**).

The baseline characteristics of patients with TILs ≥30% and <30% are shown in **Table 1**. The median age in the TILs ≥30% and <30% groups was 64 and 62 years, respectively. The majority of patients in both groups were postmenopausal, and stage II TNBC was the most common stage at diagnosis. No significant differences in clinical or pathological characteristics, including tumor stage, nodal stage, histological subtype, and lymphovascular invasion, were observed between the two groups, except for tumor grade. Grade 3 tumors were significantly more frequent in the TILs ≥30% group than in the TILs <30% group (p=0.042). Adjuvant chemotherapy was administered to 90.7% of patients with TILs ≥30% and to 81.18% with TILs <30% (p=0.203). Chemotherapy was omitted in 20 patients (15.6%), typically due to advanced age (median age 80 years), comorbidities (60%), or treatment refusal. The rates of adjuvant radiotherapy were similar between the two groups (46.5% vs. 45.9%, p=1.00).

RFS according to TIL levels (≥30% vs.<30%)

Data for the RFS analysis were censored on 31 December 2024, with a median follow-up time of 83 months. Relapse occurred in 5 of 43 (11.6%) patients in the TILs ≥30% group and in 18 of 85 (21.2%) patients in the TILs <30% group. Although the difference was not significant, RFS showed a favorable trend in the TILs ≥30% group compared with the <30% group. The median RFS was not reached (NR) (HR 0.54; 95% CI, 0.20–1.49; p = 0.238) (**Figure 2**). The 5-year RFS rate was 90.7% in the TILs ≥30% group versus 80.9% in the TILs <30% group.

In subgroup analyses, patients with TILs ≥30% consistently demonstrated a favorable trend in RFS compared with those with TILs <30% across most clinical subgroups (**Supplementary Appendix Table S1**). An exploratory analysis of the chemotherapy-naïve subgroup (n = 20) was underpowered and did not allow definitive

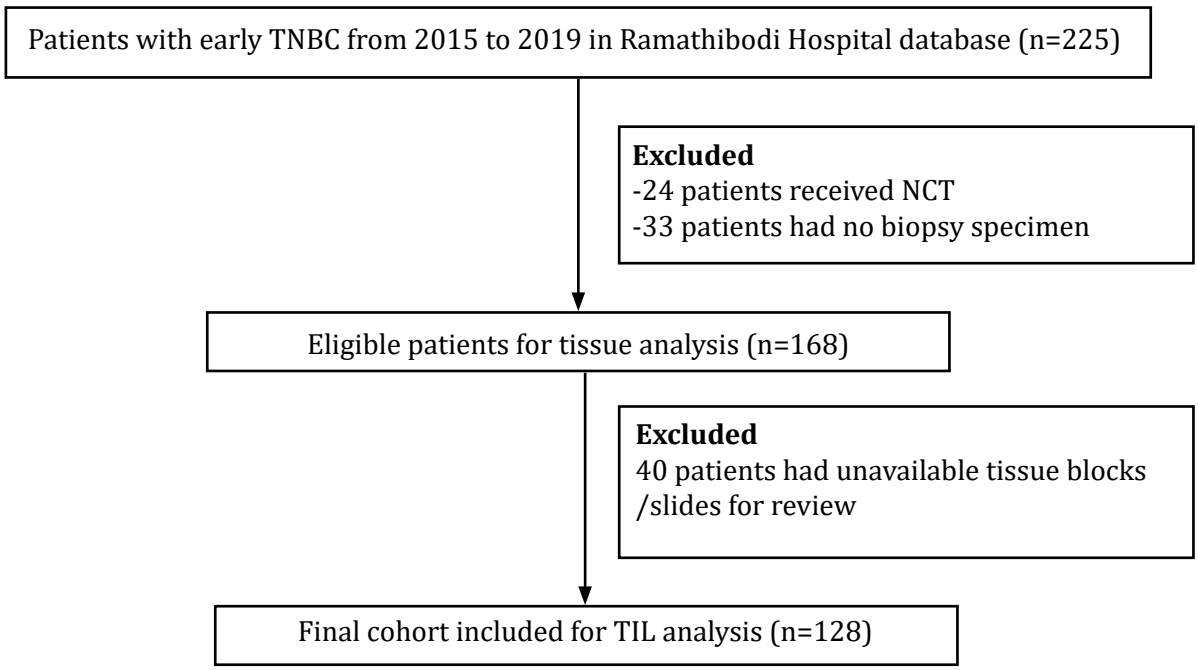


Figure 1. Patient consort diagram

Abbreviations: TNBC, triple-negative breast cancer; NCT, neoadjuvant chemotherapy; TILs, tumor-infiltrating lymphocytes.

Table 1. Baseline characteristics (TIL levels≥30% vs. <30%)

	TIL levels in patients		Total (n=128)	*p*- value
	≥30% (n=43)	<30% (n=85)		
Age, years				
Mean (SD)	61.4 (13.7)	64.15 (12.26)	63.24 (12.78)	
Median (range)	64.0 (38.0–93.0)	62.0 (31.0–95.0)	63.0 (31.0–95.0)	
Menopausal status				0.570
Pre-menopause	20 (46.51)	34 (40.00)	54 (42.19)	
Post-menopause	23 (53.49)	51 (60.00)	74 (57.81)	
Comorbidities				0.425
HT	11 (25.58)	18 (21.18)	29 (22.66)	
Diabetes mellitus	4 (9.30)	9 (10.59)	13 (10.16)	
Dyslipidemia	9 (20.93)	10 (11.76)	19 (14.84)	
No comorbidities	27 (62.79)	60 (70.59)	87 (67.97)	
ECOG Performance Status				0.482
0	38 (88.37)	71 (83.53)	109 (85.16)	
1	4 (9.30)	13 (15.29)	17 (13.28)	
2	1 (2.33)	1 (1.18)	2 (1.56)	
Stage				0.468
I	11 (25.58)	27 (31.76)	38 (29.69)	
II	25 (58.14)	50 (58.82)	75 (58.59)	
III	7 (16.28)	8 (9.41)	15 (11.72)	

Table 1. Baseline characteristics (TIL levels ≥30% vs. <30%)

	TIL levels in patients		Total (n=128)	*p*- value
	≥30% (n=43)	<30% (n=85)		
pT Stage				0.660
T1	16 (37.21)	33 (38.83)	49 (38.28)	
T2	23 (53.49)	48 (56.47)	71 (55.47)	
T3	4 (9.30)	3 (3.53)	7 (5.47)	
T4	0 (0)	1 (1.8)	1 (0.78)	
Lymph node				0.394
N0	28 (65.12)	63 (74.12)	91 (71.09)	
N1	8 (18.60)	16 (18.83)	24 (18.75)	
N2	4 (9.30)	2 (2.35)	6 (4.69)	
N3	3 (6.98)	4 (4.71)	7 (5.47)	
Histological subtype				0.135
Infiltrating ductal carcinoma	34 (79.07)	70 (82.35)	104 (81.25)	
Infiltrating ductal and lobular carcinoma	5 (11.63)	3 (3.53)	8 (6.25)	
Others	4 (9.30)	12 (14.12)	16 (12.50)	
Grade				0.042
1	0 (0)	1 (1.18)	1 (0.78)	
2	4 (9.30)	22 (25.88)	26 (21.31)	
3	36 (83.72)	56 (65.88)	92 (71.88)	
Unknown	3 (6.98)	6(7.06)	9(7.03)	
LVI				0.442
Positive	14 (32.56)	35 (41.18)	49 (38.28)	
Negative	29 (67.44)	50 (58.82)	79 (61.72)	
Adjuvant CMT				0.203
Yes	39 (90.70)	69 (81.18)	108 (84.38)	
No	4 (9.30)	16 (18.82)	20 (15.63)	
CMT regimen				0.795
Anthracycline	37 (86.05)	65 (76.47)	102 (79.69)	
Taxane	17 (39.53)	26 (30.59)	43 (33.59)	
Adjuvant RT				1.000
Yes	20 (46.51)	39 (45.88)	59 (46.09)	
No	23 (53.49)	46 (54.12)	69 (53.91)	

Data are n (%) unless otherwise specified.

Abbreviations: TILs, tumor-infiltrating lymphocytes; SD, standard deviation; HT, hypertension; pT, pathological tumor stage; LVI, lymphovascular invasion; CMT, chemotherapy; RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group

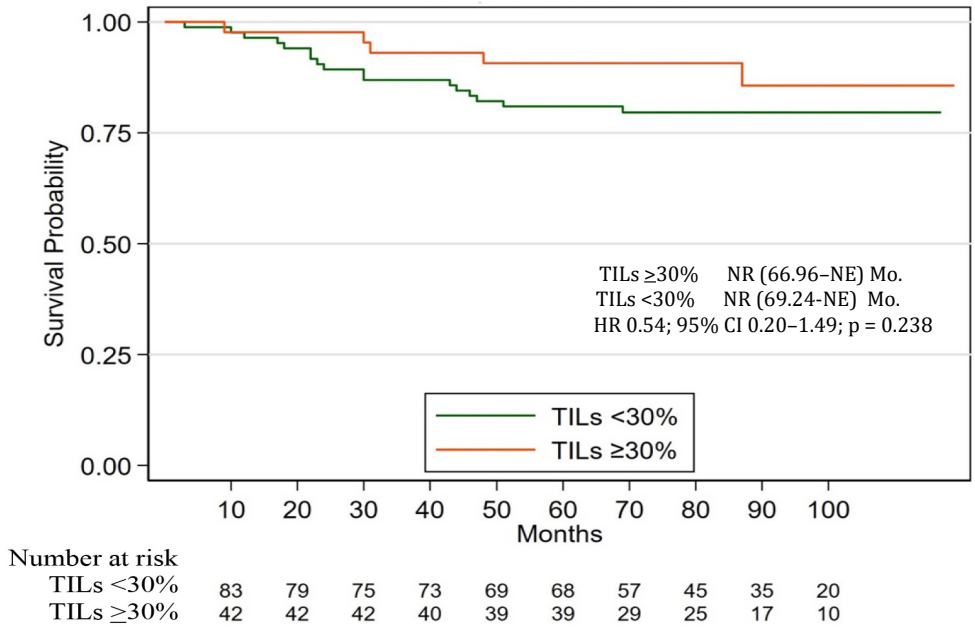


Figure 2. Kaplan–Meier curve of RFS stratified by TIL levels.

Patients with TILs >30% were compared with those with TILs <30%. Data in parentheses are 95% confidence intervals.

Abbreviations: Mo., months; NE, not estimated; NR, not reached; RFS, relapse-free survival; TILs, tumor-infiltrating lymphocytes.

conclusions. Nonetheless, the variability in treatment highlights potential selection bias and may partly explain the attenuation of the prognostic effect of TILs in this cohort.

RFS According to TIL Levels (≥20% vs. <20% and ≥10% vs. <10%)

The median RFS for TIL cutoff values ≥20% and <20% was NR in both groups, with an HR of 1.05 (95% CI, 0.45–2.40). Similarly, the median RFS for TILs ≥10% and <10% were NR, with an HR of 0.99 (95% CI, 0.36–2.68) (**Figures 3A and B**)

BCSS and OS according to TIL levels (≥30% vs. <30%)

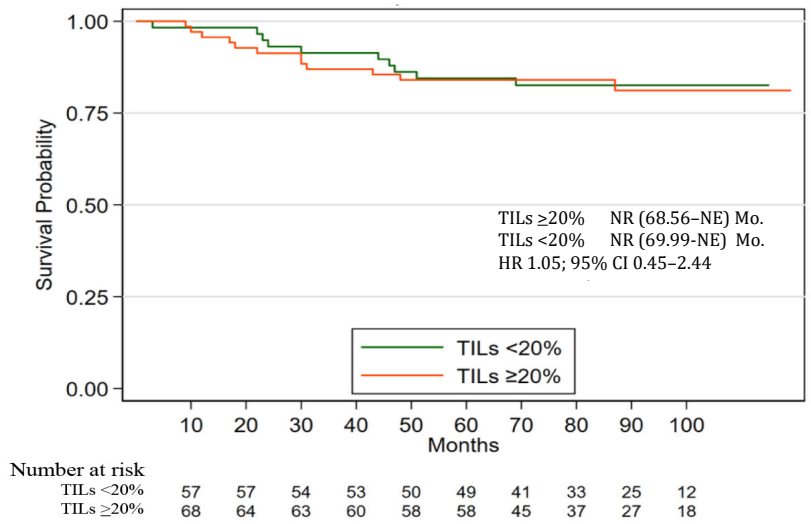
Among the 128 patients, 18 deaths occurred—12 from breast cancer and six from other causes. The median BCSS was NR in either group. Patients with TILs ≥30% tended to have longer breast cancer–specific survival (HR, 0.43; 95% CI, 0.09–1.97) (**Figure 4**). OS was also NR in either group. Patients with TILs ≥30% showed a lower risk of death from any cause (HR, 0.67; 95% CI, 0.22–2.06) (**Figure 5**).

Univariate and multivariate analyses of relapse-free survival

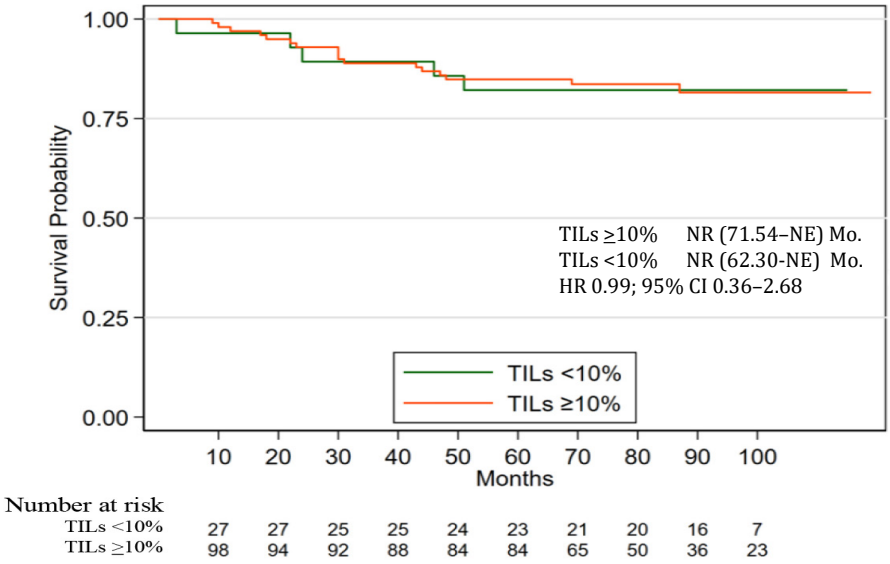
The univariate analysis identified the stage at diagnosis as a factor associated with RFS. However, in the multivariate analysis, adjusting for potential confounding factors, no variables were significantly associated with RFS. Notably, a TIL cutoff ≥30% was not associated with RFS in the univariate or multivariate analysis (**Table 2**).

Discussion

We conducted a retrospective study of patients with resectable TNBC at a tertiary cancer center in Thailand to evaluate the prognostic role of TILs. Patients with TIL levels ≥30% showed a favorable trend toward improved RFS, BCSS, and OS, although these associations did not reach statistical significance, likely due to limited statistical power and event rates. While higher TIL levels are associated with improved clinical outcomes, the independent prognostic value of TILs remains inconclusive within our cohort. The long median follow-up of 83 months largely reflects patients diagnosed earlier, which may have reduced the power to detect survival differences.



(A)



(B)

Figure 3. Kaplan–Meier curves of RFS stratified by different TIL cutoffs

(A) RFS according to TILs ≥ 20% vs. <20%. **(B)** RFS according to TILs ≥10% vs. <10%. Data in parentheses are 95% confidence intervals.

Abbreviations: Mo., months; NE, not estimated; NR, not reached; RFS, relapse-free survival; TILs, tumor-infiltrating lymphocytes.

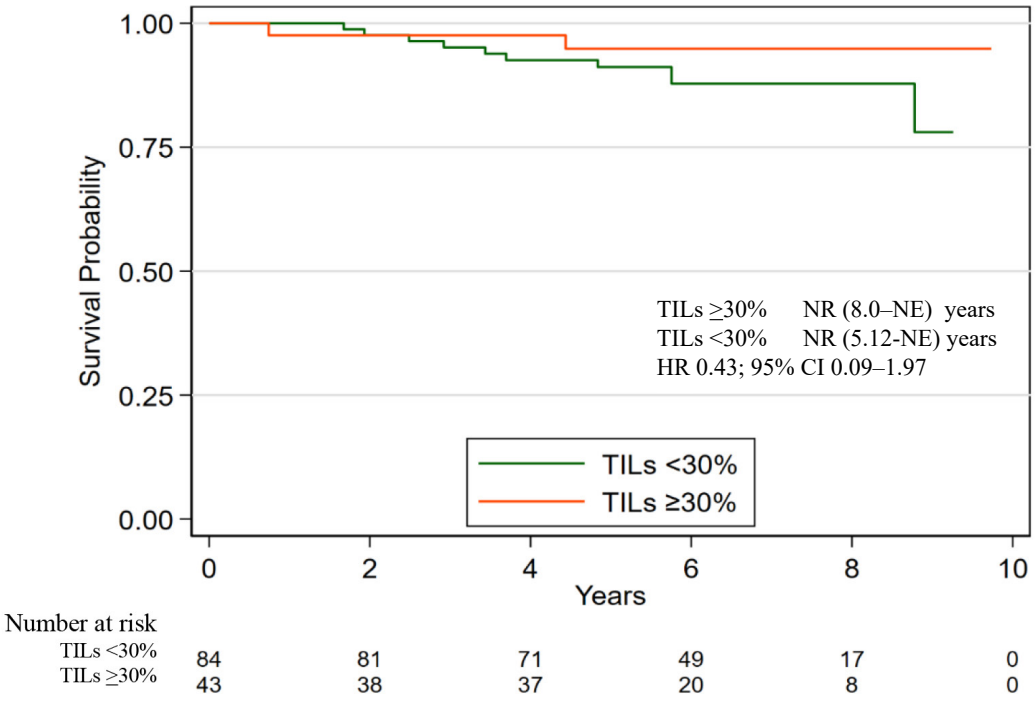


Figure 4. Kaplan–Meier curve of breast cancer-specific survival stratified by TIL levels ≥30% vs. <30%.

Data in parentheses are 95% confidence intervals.

Abbreviations: NE, not estimated; NR, not reached; BCSS, breast cancer-specific survival; TILs, tumor-infiltrating lymphocytes.

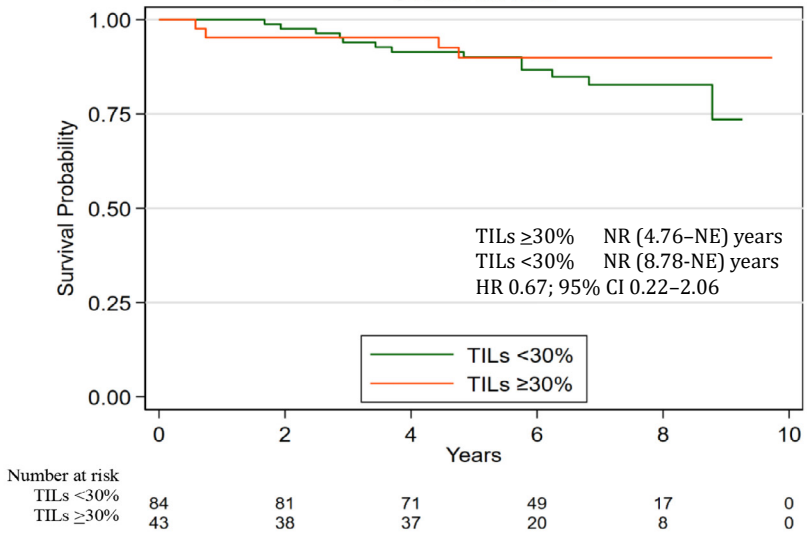


Figure 5. Kaplan–Meier curve of overall survival stratified by TIL levels ≥30% vs. <30%. Data in parentheses are 95% confidence intervals.

Abbreviations: NE, not estimated; NR, not reached ; TILs, tumor-infiltrating lymphocytes.

Table 2. Univariate and multivariate analyses of relapse-free survival

Characteristics	Univariate HR (95% CI)	*p*-value	Multivariate HR (95% CI)	*p*-value
TILs ≥30%	0.54 (0.20–1.49)	0.238	0.39 (0.13–1.16)	0.091
Stage (per 1 stage)	2.35 (1.18–4.71)	0.015	7.41 (0.52–105.64)	0.140
pN (per 1 N stage)	1.27 (0.93–1.72)	0.130	2.69 (0.23–31.96)	0.434
pT (per 1 T stage)	1.17 (0.68–2.02)	0.565	0.28 (0.01–7.62)	0.453
Grade (per 1 grade)	0.97 (0.37–2.57)	0.959	N/A	
LVI	1.14 (0.49–2.67)	0.758	N/A	
Adjuvant systemic treatment	0.82 (0.24–2.78)	0.752		
RT	0.79 (0.34–1.86)	0.593	N/A	
Ki67 (per 1 %)	1.00 (0.98–1.01)	0.714	N/A	
Age (per 1 year)	1.00 (0.96–1.03)	0.782	N/A	

Abbreviations: HR, hazard ratio; CI, confidence interval; TILs, tumor-infiltrating lymphocytes; pT, pathological tumor stage; pN, pathological nodal stage; LVI, lymphovascular invasion; RT, radiotherapy; N/A, not applicable.

We specifically assessed stromal TILs, which are more reproducible than intratumoral TILs and are recommended for standardized evaluation in TNBC.[15, 17, 18] Although no universally accepted cutoff has been established, prior studies suggest that the median TIL level in TNBC is around 15%.[19] For our primary analysis, we selected a threshold of 30% to represent a high TIL level, consistent with the International TILs Working Group 2014 guidelines and several supporting studies.[14, 19-21] Other thresholds, such as 10% [13, 22], 20%[18], and even ≥ 50%,[21] have also been proposed, but very few of our patients had TILs ≥ 50%, precluding meaningful analysis.

In our cohort, 15.6% of patients did not receive systemic treatment, reflecting real-world clinical practice. Although treatment heterogeneity may potentially attenuate the prognostic impact of TILs, this effect was likely limited in our study, as the proportion of patients who did not receive systemic therapy was comparable between the TIL ≥30% and TIL <30% groups.

Recent research from Colombia found that patients with high TIL levels were more often diagnosed at earlier clinical stages (I/II), had smaller tumor sizes, and no nodal involvement than those with low TIL levels.[22] In contrast, although our cohort was also predominantly stage I–II, we found no significant differences in tumor size or nodal status between TILs <30% and TILs ≥30%. The only significant association was the tumor grade, which was higher in patients with TILs ≥30%. This is consistent with findings by Leon-Ferre et al.,[19] who reported that high TIL levels correlated with higher tumor grade but not with tumor size or nodal status in cohorts from North America, Europe, and parts of Asia. Previous studies have also shown that well-differentiated tumors tend to have lower TIL levels.[23, 24] These findings suggest potential biological or ethnic differences that merit further investigation in Eastern populations.

Our results suggest that high TIL levels are associated with favorable survival outcomes, consistent with findings from multiple previous Western studies.[13, 14, 25-31] For example, Dülgar et al. reported that higher TIL levels significantly improved DFS but not OS in a Turkish TNBC cohort.[31] Loi et al. reported that every 10% increase in TILs was associated with improved BCSS.[13] Similarly, a 2012 meta-analysis showed a positive correlation between TIL levels and OS and DFS in TNBC.[32] More recently, a systematic review and meta-analysis including patients treated with neoadjuvant chemotherapy confirmed that higher TIL expression was significantly associated with better DFS and OS.[33] In addition, data from Vietnam involving 105 patients showed that high TIL levels and elevated CD8+ intratumoral TILs were associated with improved prognosis in early-stage TNBC.[34]

Using multivariate analysis, TIL levels were not independently associated with improved RFS, whereas breast cancer stage remained a stronger prognostic factor. This finding may be explained by several factors, including variability in TIL assessment, treatment heterogeneity, and the predominance of patients receiving adjuvant chemotherapy, which may have attenuated the independent effect of TILs. In addition, the modest sample size, limited number of relapse events, and imbalance between TIL groups may have reduced statistical power, contributing to the lack of statistically significant findings. In contrast, larger studies, including those from Asian populations, have demonstrated a significant association between high TIL levels and improved clinical outcomes, including RFS, OS, and BCSS.[35] These discrepancies highlight the need for larger, adequately powered studies to better define the prognostic role of TILs.

To the best of our knowledge, this is the largest cohort study in Southeast Asia to evaluate the prognostic significance of TIL levels in resectable TNBC. Our study, therefore, addresses a critical gap in the global TNBC literature by adding data from an underrepresented Southeast Asian population. The assessment of TILs is practical, as it can be performed on routine H&E-stained sections without additional testing. Unlike molecular assays that are often unavailable or unaffordable in low- and middle-income countries, TIL assessment is inexpensive and can be readily integrated into daily pathology practice, making it particularly relevant for Southeast Asian health systems.

However, limitations of our study include its retrospective single-center design, modest sample size, and the subjectivity of TIL evaluation. The modest sample size and imbalance between TIL groups may have limited statistical power and contributed to the lack of statistically significant findings. Emerging methodologies, such as tissue microarray analysis, flow cytometry, and gene expression profiling, may offer more objective and standardized approaches for evaluating immune infiltration in future studies.[36]

With immunotherapy increasingly incorporated into the management of early-stage and advanced TNBC, TILs may serve not only as prognostic markers but also as predictive biomarkers to guide treatment decisions. Our findings provide a foundation for future multi-institutional collaborations and prospective trials across Asia to validate the role of TILs in the modern immunotherapy landscape.

Conclusion

Higher TIL levels (≥30%) were associated with a favorable trend in survival outcomes but did not reach statistical significance. This study provides real-world evidence from a Southeast Asian cohort with long-term follow-up, highlighting the feasibility of TIL assessment in routine clinical practice. Larger, adequately powered prospective studies are needed to further define the prognostic role of TILs in resectable TNBC.

Acknowledgement

The authors would like to thank the Ramathibodi Cancer Registry Unit of the Ramathibodi Comprehensive Cancer Center for support with clinical data.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

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

References

1. Srimuninnimit V, Chaiyapan W, Thiravud K, Waisayarat J, Thongyoo P, Leelarungrayub N, et al. Real-life clinical pattern, management, and survival in Thai patients with early-stage or metastatic triple-negative breast cancer. PLOS ONE 2018; 13: e0209040.
2. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet 2021; 397: 1750–69.
3. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. New Engl J Med 2010; 363.
4. Jiang YZ, Ma D, Suo C, Shi J, Xue M, Hu X, et al. Genomic and transcriptomic landscape

of triple-negative breast cancers: subtypes and treatment strategies. Cancer Cell 2019; 35: 428–40.e5.
5. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res 2015; 21: 1688-98.
6. Bareche Y, Venet D, Ignatiadis M, Aftimos P, Piccart M, Rothe F, et al. Unravelling triple-negative breast cancer molecular heterogeneity using an integrative multiomic analysis. Ann Oncol 2018; 29: 895-902.
7. Marra A, Trapani D, Viale G, Criscitiello C, Curigliano G. Practical classification of triple-negative breast cancer: intratumoral heterogeneity, mechanisms of drug resistance, and novel therapies. NPJ Breast Cancer 2020; 6: 54.
8. Bianchini G, De Angelis C, Licata L, Gianni L. Treatment landscape of triple-negative breast cancer: expanded options and evolving needs. Nat Rev Clin Oncol 2022; 19: 91–113.
9. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015; 26: 259-71.
10. Goto W, Kawaguchi K, Nagao T, Koyama H, Kitano S, Miyashita M, et al. Predictive value of improvement in the immune tumour microenvironment in patients with breast cancer treated with neoadjuvant chemotherapy. ESMO Open 2018; 3: e000305.
11. Asano Y, Kobayashi S, Yamashita T, Sueta A, Takao S, Nomura Y, et al. Prediction of treatment response to neoadjuvant chemotherapy in breast cancer by subtype using tumor-infiltrating lymphocytes. Anticancer Res 2018; 38: 2311-21.
12. Ruan M, Zhao X, Li W, Shi W, Wang Y, Cao S. Predictive value of tumor-infiltrating lymphocytes to pathological complete response in neoadjuvant treated triple-negative breast cancers. Diagn Pathol 2018; 13.
13. Loi S, Drubay D, Adams S, Pruneri G, Francis PA, Lacroix-Triki M, et al. Tumor-infiltrating lymphocytes and prognosis in early-stage triple-negative breast cancer: a pooled analysis. J Clin Oncol 2019; 37: 559–69.
14. de Jong VMT, Wang Y, Ter Hoeve ND, Opdam M, Stathonikos N, Jóźwiak K, et al. Prognostic value of stromal tumor-infiltrating lymphocytes in young, node-negative, triple-negative breast cancer without systemic therapy. J Clin Oncol 2022; 40: 2361–74.
15. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, et al. Tumor-infiltrating lymphocytes and prognosis in breast cancer subtypes: a pooled analysis of 3,771 patients. Lancet Oncol 2018; 19: 40-50.
16. El Bairi K, Haynes HR, Blackley E, Fineberg S, Shear J, Turner S, et al. The tale of TILs in breast cancer: A report from The International Immuno-Oncology Biomarker Working Group. NPJ Breast Cancer 2021; 7: 150.
17. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015; 26: 259-71.
18. Suwannaphoom K SS, Wiwatwarayos K, Seneetuntigul P, Julimasart P. Assessing the relationship between tumor-infiltrating lymphocytes and PD-L1 expression in triple negative breast cancer: Identifying optimal TILs cut-off value for pathologic reporting. Ann Diag Pathol 2024; 70: 152294.
19. Leon-Ferre RA, Jonas SF, Salgado R, Loi S, de Jong V, Carter JM, et al. Tumor-infiltrating lymphocytes in triple-negative breast cancer. JAMA Oncol 2024; 331: 1135–44.
20. Geurts VCM, Balduzzi S, Steenbruggen TG, Linn SC, Siesling S, Badve SS, et al. Tumor-infiltrating lymphocytes in stage I triple-negative breast cancer untreated with chemotherapy. JAMA Oncol 2024; 10: 1077–86.
21. Tramm T, Di Caterino T, Jylling AB, Lelkaitis G, Lænkholm AV, Ragó P, et al. Standardized assessment of tumor-infiltrating lymphocytes in breast cancer: an evaluation of inter-observer agreement between pathologists. Acta Oncol 2017; 56: 1067-73.
22. Huertas-Caro CA RM, Rey-Vargas L, Bejarano-Rivera LM, Ballen DF, Nuñez M,

Mejía JC, et al. Tumor infiltrating lymphocytes (TILs) are a prognosis biomarker in Colombian patients with triple negative breast cancer. Sci Rep 2023; 13.
23. Park HS, Heo I, Kim JY, Kim S, Nam S, Park S, et al. No effect of tumor-infiltrating lymphocytes (TILs) on prognosis in patients with early triple-negative breast cancer: Validation of recommendations by the International TILs Working Group 2014. J Surg Oncol 2016; 114: 17-21.
24. Savas P, Salgado R, Denkert C, Sotiriou C, Darcy PK, Smyth MJ, et al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. Nat Rev Clin Oncol2016; 13: 228-41.
25. Gao G, Wang Z, Qu X, Zhang Z. Prognostic value of tumor-infiltrating lymphocytes in patients with triple-negative breast cancer: a systematic review and meta-analysis. BMC Cancer 2020; 20: 179.
26. Jang N, Kwon HJ, Park MH, Kang SH, Bae YK. Prognostic value of tumor-infiltrating lymphocyte density assessed using a standardized method based on molecular subtypes and adjuvant chemotherapy in invasive breast cancer. Ann Surg Oncol 2018; 25: 937-46.
27. Gu-Trantien C, Loi S, Garaud S, Equeter C, Libin M, de Wind A, et al. $CD4^+$ follicular helper T cell infiltration predicts breast cancer survival. J Clin Invest 2013; 123: 2873-92.
28. Yu X, Zhang Z, Wang Z, Wu P, Qiu F, Huang J. Prognostic and predictive value of tumor-infiltrating lymphocytes in breast cancer: a systematic review and meta-analysis. Clin Transl Oncol 2016; 18: 497-506.
29. Stanton SE, Disis ML. Clinical significance of tumor-infiltrating lymphocytes in breast cancer. J ImmunoTher Cancer 2016; 4: 59.
30. Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, Kazkaz GA. The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: A meta-analysis. Breast Cancer Res Treat 2014; 148: 467-76.
31. Dulgar O, Ilvan S, Turna ZH. Prognostic factors and tumor infiltrating lymphocytes in triple negative breast cancer. Eur J Breast Health 2020; 16: 276-81.
32. Dieci MV, Tsvetkova V, Orvieto E, Piacentini F, Ficarra G, Griguolo G, et al. Immune characterization of breast cancer metastases: prognostic implications. BMC Cancer 2020; 20: 256.
33. de Moraes FCA, Souza MEC, Sano VKT, Moraes RA, Melo AC. Association of tumor-infiltrating lymphocytes with clinical outcomes in patients with triple-negative breast cancer receiving neoadjuvant chemotherapy: a systematic review and meta-analysis. Clin Transl Oncol. 2025; 27: 974-87.
34. Hoang H, Phung H, Tung NN, Dinh TN, Nguyen T, Nguyen T. The role of tumor-infiltrating lymphocytes in triple-negative breast cancer in Vietnam. International Journal of Gynecologic Cancer 2023; 33(Suppl 3): A87-A8.
35. Han E, Choi HY, Kwon HJ, Chung YR, Shin HC, Kim EK, et al. Characterization of tumor-infiltrating lymphocytes and their spatial distribution in triple-negative breast cancer. Breast Cancer Res. 2024; 26: 180.
36. Shen Y, Peng X, Shen C. Identification and validation of immune-related lncRNA prognostic signature for breast cancer. Genomics 2020; 112: 2640-6.