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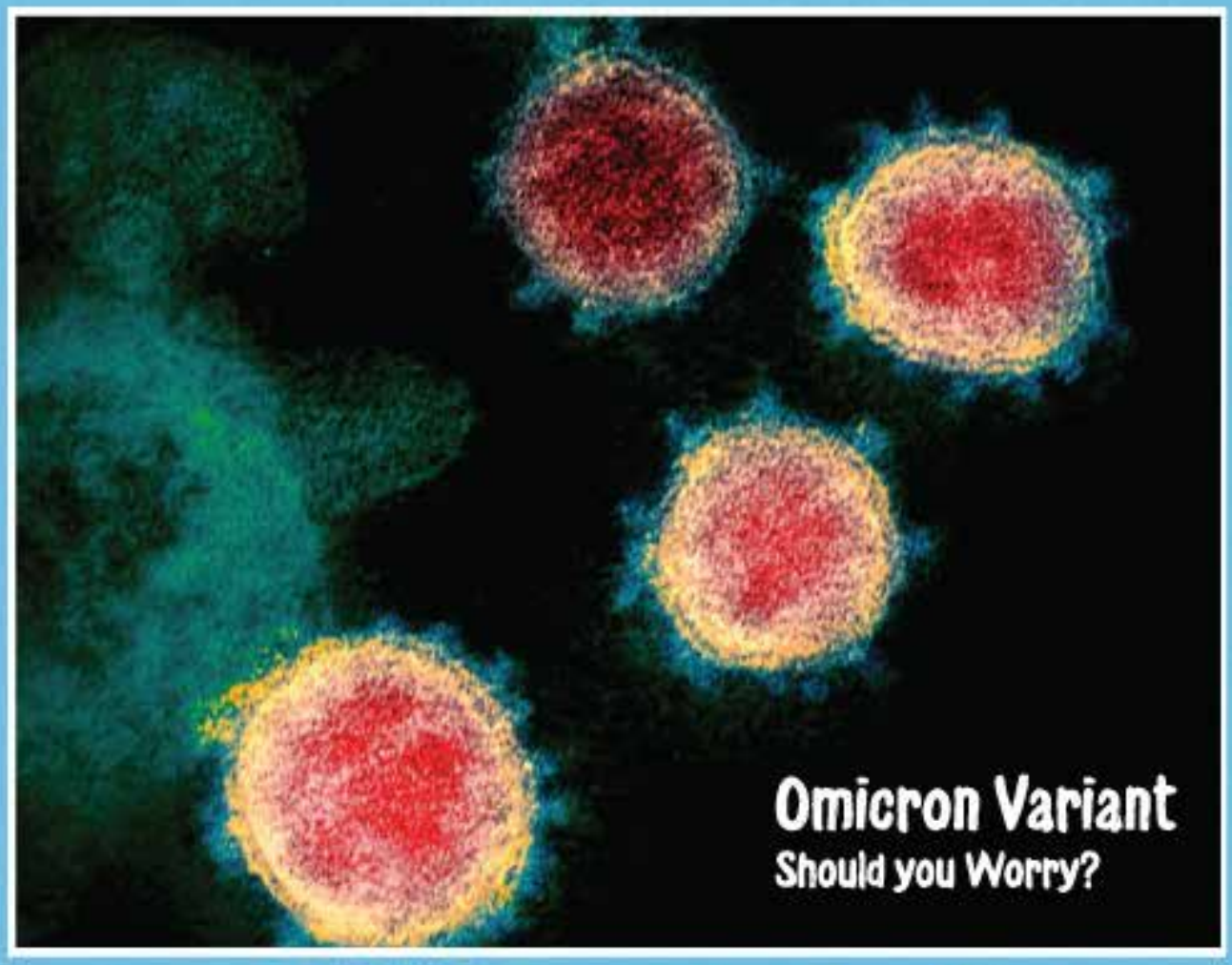

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Predictive and Prognostic Value of Tumor– Infiltrating Lymphocytes for Pathological Response to Neoadjuvant Chemotherapy in Triple Negative Breast Cancer

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Abstract

Background: Tumor–infiltrating lymphocytes (TILs) reflect the antitumor response of the host. This study aimed to assess the value of TILs in predicting pathological response after neoadjuvant chemotherapy (NAC) and survival outcomes in patients with triple–negative breast cancer (TNBC).

Methods: A retrospective analysis conducted between February 2012 and December 2015. Patients with stage I, II, and III TNBC patients were enrolled. TILs were assessed in haematoxylin and eosin–stained sections from true cut needle biopsies before NAC. According to international TILs working group, we had three groups; low (0–10%), intermediate (11–59%), and high TILs (≥ 60%).

Results: A total of 159 patients was included, 56% were premenopausal and 76.1% were less than 60 years. The main bulk of patients had histological grade III, high Ki 67, and high TILs (74.2%, 84.3%, and 72.3%), respectively. The pre–treatment high TILs was significantly correlated with high Ki–67 ($p = 0.001$), pCR ($p < 0.001$), and late relapse ($p < 0.001$). Other clinico–pathological features such as age, menopausal status, tumor size, histological grade, lymph node involvement and lympho–vascular invasion weren't significantly correlated with TILs levels. 71.3% of enrolled patients having high TILs achieved pCR, vs 27.8% in the intermediate group and 30.8% in low group. After a median follow–up of 45.3 months, patients with high TILs were significantly associated with longer DFS and OS as compared to intermediate and low TILs (27.2 vs 15.9 vs11.4 months for DFS and 70.2 vs 34.3 vs 27.6 months for OS) $p<0.001$).

Conclusions: Pre–treatment level of TILs had a predictive and prognostic value in TNBC patients receiving NAC. TILs may be integrated into the basic laboratory for TNBC prognostication as a credible biomarker.

Keywords: triple negative breast cancer – neoadjuvant chemotherapy – pathological response– tumor–infiltrating lymphocytes.

Introduction

Although the progress of personalized therapeutic strategies in triple–negative breast cancer (TNBC), most of cases even in early stage relapsed soon. For example, the –5year relapse–free survival (RFS) rate for T1N0–1 is approximately 85%. The aggressive disease behaviour and lack of adequate target therapy mandated the need for new biomarkers that could guide therapy selection[(1)].

Nowadays, many data confirmed the role of immunotherapy in the management of TNBC, however, most of these therapies are not available in most of oncology centers in our countries due to economic issues. Consequently, still combined chemotherapy is the cornerstone of all treatment protocols[(2)].

The utilization of neoadjuvant regimens is increasing to optimize the complete pathological response (pCR) which will be reflected in the prediction of survival outcome. Plentiful studies either retrospective or prospective have

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been proved that pCR is the most important prognostic factor after neoadjuvant chemotherapy (NAC) in patients with breast cancer (BC). Therefore, it represents a proper representative end–point for long–term outcomes[3]. Achieving pCR after surgery correlates with a statistically significant improvement in DFS[4–6].

Tumor–infiltrating lymphocytes (TILs) are immune cells, either T cells or B cells or both, polymorph nuclear and mononuclear in variable proportions. They moved from the bloodstream to infiltrate and/or surround malignant cells[7]. They have associated with improved prognosis in different malignant types such as ovarian cancer, lung, and colon cancer. Historically, BC was considered immunologically inactive, especially in comparison with melanoma[8]. However, growing evidence from many researches demonstrated that TILs are decisive for inhibiting tumor progression[9].

This study aimed to evaluate the predictive and prognostic value of TILs after NAC in patients with TNBC.

Materials and Methods

Eligibility criteria and sample size

A total of 159 TNBC patients with stage I, II, and III treated with NAC followed by surgery were enrolled in the current study from the Department of Medical Oncology and General Surgical Department, Faculty of Medicine, Zagazig University, Egypt between February 2012 to December 2015. The eligibility criteria were pathologically diagnosed with TNBC, good performance status (ECOG 0–2), adequate organ reservoir, no prior chemotherapy or radiotherapy, measurable diseases, adequate tissue blocks (formalin–fixed and paraffin–embedded), and follow–up information.

Data collection and ethical aspect

Demographic and pathological features were collected by chart review. Owing to the retrospective nature of the study, there was no written consent. The study was approved by The institutional review board (IRB).

Staging system

The initial work–up and the pathologic staging were based on NCCN guideline 2012 and the Joint Committee on Cancer (AJCC) for BC, 7th edition.

Immunohistochemistry technique

A pre–therapeutic true cut biopsy was obtained for pathological diagnosis and immunohistochemistry (IHC) analysis. TNBC is defined by <1% of cells staining for estrogen receptor (ER) and progesterone receptor (PR) expression and by negative over–expression/amplification of HER2/neu.

Haematoxylin and eosin (H&E) stained were used for TILs evaluation by standard methods according to international TILs working group (intensitythe percentage of TILs infiltrates). Accordingly, we had three groups; low (0–10%), intermediate (11–59%), and high TILs (60%)[10].

Response evaluation

After NAC, the pathological response was classified into the pCR which referred to the absence of invasive residual in the breast or nodes. While the presence of residual was considered non pCR.

Treatment protocol

The treatment regimen was institutionally based. Organ reservoir evaluation in the form of liver, kidney functions and complete blood count was requested. Upon completion of the pre–planned protocol, the patients underwent breast surgery (modified radical mastectomy or breast conservative according to the current situation). The treatment flow chart illustrated in figure 1.

Follow up

For all the eligible patients, physical examination/ 3–month. Mammography performed annually. Other investigations in the form of CT, MRI, bone scan, or tumor markers had no role in asymptomatic cases, upon clinical suspicion. The date of the last follow–up was October 2019.

Statistical analysis

The correlation between TILs and demographic features were analysed using chi–squared tests. DFS was calculated from the interval between the diagnosis date to the proved recurrent event date. The OS was measured from diagnosis date of death or the last follow up date. The OS and DFS were calculated by The Kaplan–Meier method. P – value below 0.05 was considered significant.

Results

The basic features of the included patients

A total of 159 patients with stage I, II, and III TNBC were eligible. Among these patients, 56% were premenopausal and 76.1% were less than 60 years old at the time of diagnosis. The main bulk of our patients had histological grade III, high Ki 67, and high TILs (74.2%, 84.3%, and 72.3%), respectively. 95 (69.7%) patients achieved pCR. The main clinical–pathological features are summarized in table 1. Photomicrographs of low, intermediate, and high TILs showed in Figure 2 (A, B, and C) respectively.

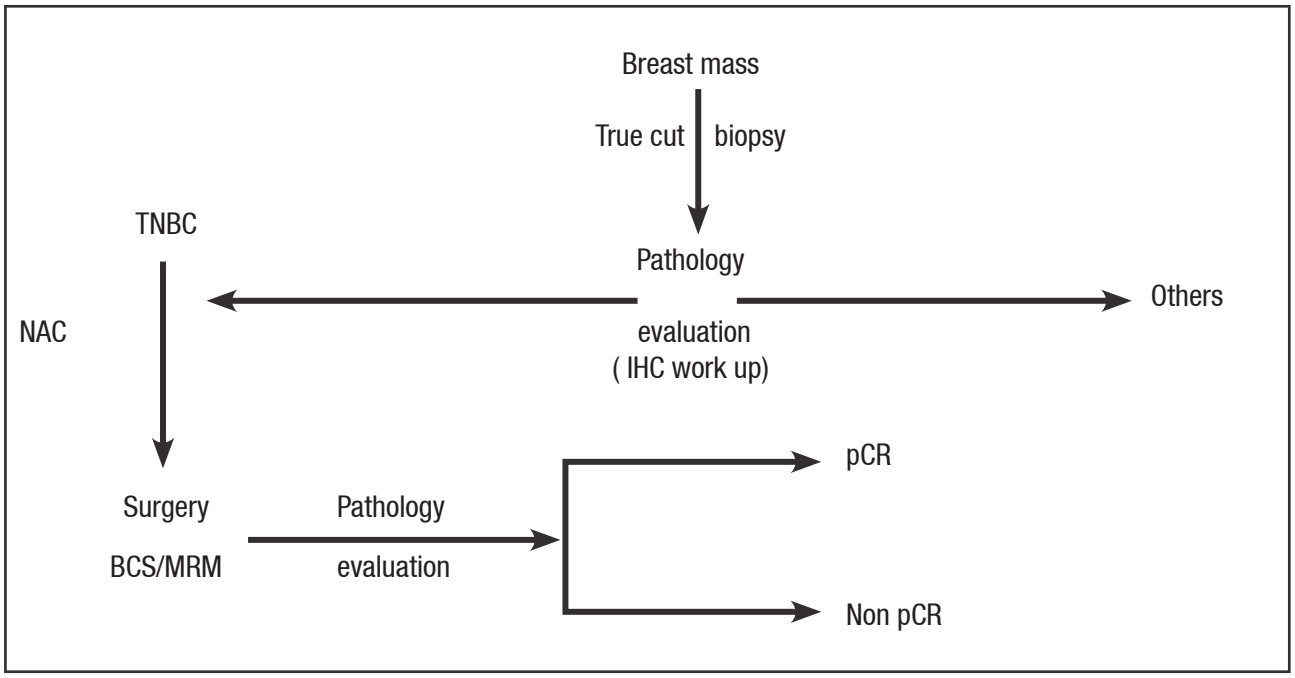

Figure 1: Treatment flow chart.
TNBC: triple negative breast cancer, IHC: immunohistochemistry, NAC: neoadjuvant chemotherapy (4–6 cycles), MRM: modified radical mastectomy, BCS: breast conserving surgery, pCR: complete pathological response.

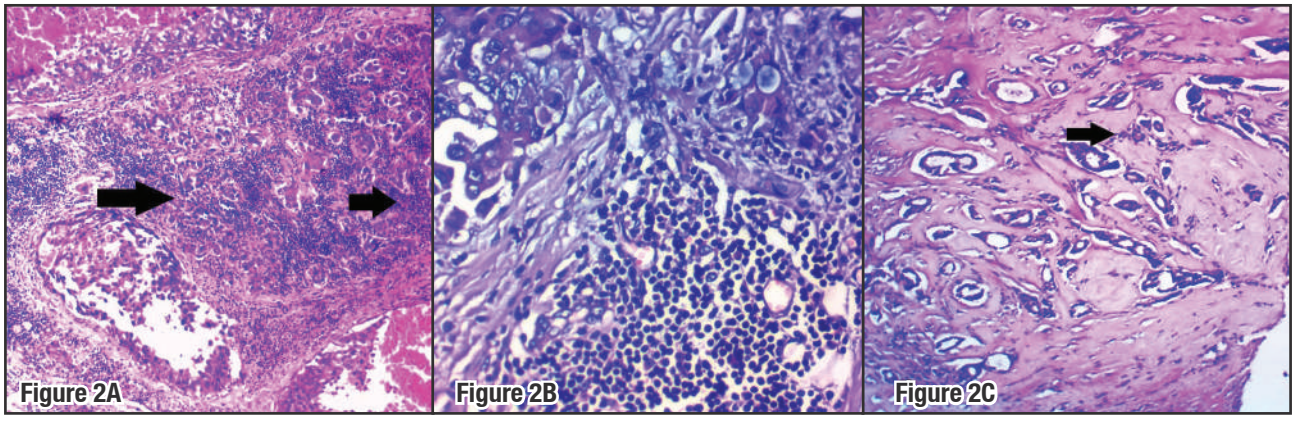

Figure 2: Photomicrographs of low (0–10%), intermediate (11–59%), and high TILs (≥ 60%); A, B, and C, respectively. Immunohistochemistry X 400.

The correlation between TILs and clinic–pathological features

The results of analysis according to TILs levels are presented in table 2. The pre–treatment high level of TILs (=>60%) was significantly correlated with high Ki 67 ($p = 0.001$), pCR, late relapse, favourable outcome ($p < 0.001$ for both) and borderline significantly correlated with the age less than 60 years. Other clinic–pathological features, including tumor size, histological grade, lymph node involvement, lympho–vascular invasion, and menopausal state weren't significantly correlated with the TILs level.

The survival analysis

The median follow–up period was 45.3 months (range, 18.7–70.6 months), 128 (80.5%) patients experienced late relapse, and disease–related death was observed in 38 (23.9%) patients. Kaplan–Meier curve showed that patients with high TILs were significantly associated with better DFS and OS than those in intermediate or low TILs (27.2 vs 15.9 vs 11.4 months, and 70.2 vs 34.3 vs 27.6 months, respectively, $p<0.001$ for both) (Figure 3 A&B).

Discussion

Generally, TNBC is considered to have the most aggressive behaviour and high risk of treatment failure compared with other BC subtypes. Although its molecular heterogeneity, the NAC remains the main component of systemic therapy in early stages[11].

Refereed to many previous studies and meta–analysis, NAC and adjuvant chemotherapy are equal in the

Characteristics	Number	%	Characteristics	Number	%
Age			T1	20	12.6
<60 years	121	76.1	T2	77	48.4
=>60 years	38	23.9	T3	51	32.1
			T4	11	6.9
Menopause state			N0	10	6.3
Premenopausal	89	56	N1	60	37.7
Postmenopausal	70	44	N2	67	42.1
			N3	22	13.8
Grade			**TILs**		
I	0	0	0–10%	26	16.4
II	41	25.8	11–59%	18	11.3
III	118	74.2	=>60%	115	72.3
Pathology			**Pathological response**		
IDC	131	82.4	pCR	95	69.7
Non– IDC	28	17.6	Non– pCR	64	40.3
Multicentric			**Relapse**		
Yes	63	39.6	Early	31	19.5
No	96	60.4	Late	128	80.5
LVI			**Follow up (months)**		
Yes	72	45.3	Median	45.3	
No	78	54.7	Mean ± SD	42.9 ± 12.7	
Ki 67			**Outcome**		
Low	25	15.7	Alive	121	76.1
High	134	84.3	Died	38	23.9

Table 1: Basic features of the 159 included patients
IDC, invasive duct carcinoma; LVI, lymphovascular invasion; T, tumor size; N; lymph node status; pCR, pathological complete response; pPR, pathological partial response; TILs, tumor infiltrating lymphocytes; Early relapse, disease recurrence in the first year; Late relapse, disease recurrence after one year.

term of the OS. However, NAC has many useful benefits. The genomic analysis isn't the only predictive factor of chemotherapy response and OS in TNBC. There is a various laboratory, clinical, and pathological features[12].

TILs represent the immune system against the tumor in the surrounding microenvironment and associated with the outcome of many types of cancers. The value of TILs in metastatic TNBC, adjuvant, and neoadjuvant settings had been evaluated[8,13–19].

Among the 159 patients in the present study, high TILs (≥60%) was detected in 115 (72.3%) patients, while the intermediate and low levels were detected in 18 (11.3%) and 26 (16.4%) respectively. This result is near to the previous report by **Asano et al.**[20] who evaluated the utility and validity of TILs after NAC in 61 patients with TNBC. However, our results were not in full agreement with other studies[21–23]. These contradictions may be related to sample size, differences in patients' characteristics, and lack of a standardized method for TILs evaluation across different laboratories[24].

	TILs			
Variables	**0–10%** **No (%)**	**11–59%** **No (%)**	**=>60%** **No (%)**	**P value**
Age				
<60 years	16 (13.2)	12(9.9)	93(76.9)	0.06
=>60 years	10 (26.3)	6 (15.8)	22 (57.9)	
Menopause				
Premenopausal	12 (13.5)	8 (9.0)	69 (77.5)	0.2
Postmenopausal	14 (20.0)	12 (14.3)	46 (65.7)	
Pathology				
IDC	20 (15.3)	14 (10.7)	97 (74.0)	0.5
Non– IDC	6 (21.4%)	4 (14.3%)	18 (64.3)	
T1	2 (10.0)	2 (10.0)	16 (80.0)	
T2	10 (13.0%)	12 (15.6%)	55 (71.4%)	
T3	11 (21.6%)	4 (7.8%)	36 (70.6%)	0.2
T4	3 (27.3%)	0 (0.0)	8 (72.7%)	
N0	0 (0.0)	0 (0.0)	10 (100.0)	
N1	12 (20.0%)	8 (13.3%)	40 (66.7%)	
N2	12 (17.9%)	8 (11.9%)	47 (70.1%)	0.9
N3	2 (9.1%)	2 (9.1%)	18 (81.8%)	
Grade				
Grade II	7 (17.1%)	3 (7.3%)	31 (75.6%)	0.6
Grade III	19 (16.1%)	15 (12.7%)	84 (71.2%)	
Multicentric				
Yes	10 (15.9%)	5 (7.9%)	48 (76.2%)	0.5
No	16 (16.7%)	13 (13.5%)	67 (69.8%)	
LVI				
Yes	14 (19.4%)	9 (12.5%)	49 (68.1%)	0.5
No	12 (13.8%)	9 (10.3%)	66 (75.9%)	
Ki 67				
Low	10 (40.0%)	4 (16.0%)	11 (44.0%)	0.001
High	16 (11.9%)	14 (10.4%)	104 (77.6%)	
Pathological response				
pCR	8 (30.8%)	5 (27.8%)	82 (71.3%)	<0.001
Non– pCR	18 (69.2%)	13 (72.2%)	33 (28.7%)	
Relapse				
Early	16 (61.5%)	3 (16.7%)	12 (10.4%)	<0.001
Late	10 (38.5%)	15 (83.3%)	103 (89.6%)	
Mortality				
Alive	8 (30.8%)	4 (22.2%)	109 (94.8%)	<0.001
Died	18 (69.2%)	14 (77.8%)	6 (5.2%)	

Table 2: The correlation between TILs and clinic–pathological features

IDC, invasive duct carcinoma; LVI, lymphovascular invasion; T, tumor size; N; lymph node status; pCR, pathological complete response; pPR, pathological partial response; TILs, tumor infiltrating lymphocytes; Early relapse, disease recurrence in the first year; Late relapse, disease recurrence after one year. P value < .05 significant.

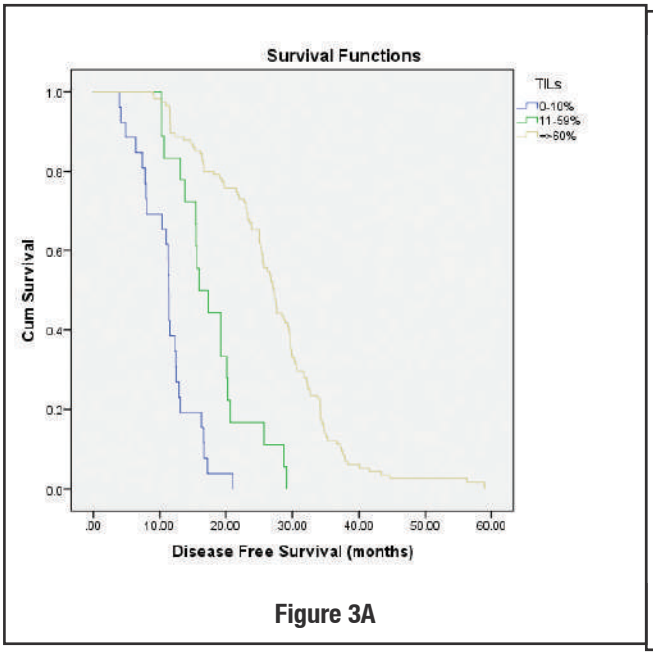

Figure 3A

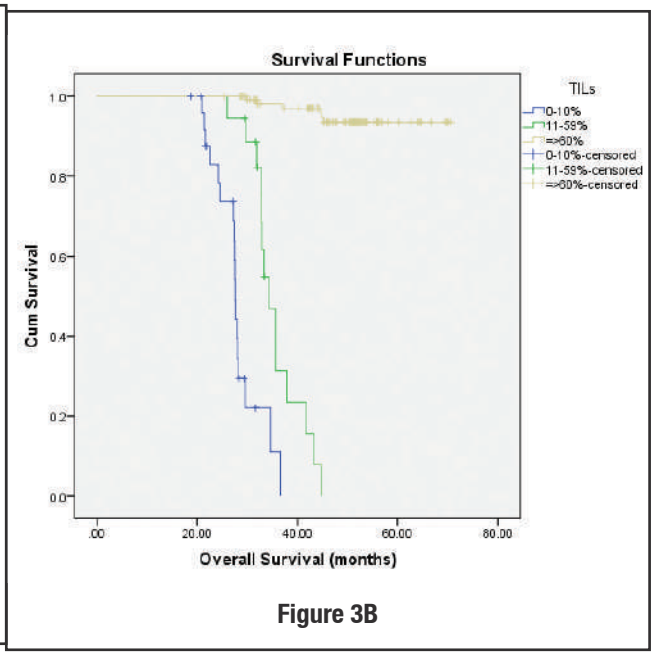

Figure 3B

Figure 3: Kaplan–Meier survival curve, stratified according to TILs. Figure 2A for disease free survival and figure 2B for overall survival.

In the current study, and after a median follow–up of 45.3 months, high pre–treatment level of TILs was associated with better response to NAC, high pCR (71.3%) and improved survival outcomes (DFS and OS were 11.4 vs 15.9 vs 27.2 months, and 27.6 vs 34.3 vs 70.2 months, for low, intermediate, and high TILs levels; p<0.001), respectively. This finding is consistent with many previous literatures. A total of 474 patients with TNBC who received NAC showed that the score of TILs was associated with pCR[25]. **West et al.**[26] reported a significant association between eight–gene expression of TILs and pCR in hormone receptor–negative BC after treatment with NAC (pCR was 74% in high TILs compared with 31% in low TILs).

A prospective trial over 300 patients included in the PREDICT study as a part of the Gepar Quinto trial, the level of TILs was an independent predictive factor of pCR in multivariate analysis[14]. **Denkert et al.**[27] confirmed the same results among TNBC patients included in the GeparSixto trial. Similarly, **Liedtke et al.**[28] through a translational subproject of the WSG–ADAPT TN trial included 336 TNBC patients' treated with NAC demonstrated higher levels of TILs were associated with better pCR.

Of note, a study of 256 patients with TNBC reported every increase in TILs by 10% associated with a decrease in the risk of both recurrence and death by 17% and 27% (p = 0.023, HR 0.83; 95 % CI 0.71–0.98 and p = 0.035, HR 0.73; 95 % CI 0.54–0.98, respectively)[21].

Moreover, **Liu et al.**[29] reported that CD8+ T–cell had a positive predictive value in TNBC (p = 0.001, HR 0.35; 95 % CI 0.23 to 0.54 and = 927). However, TILs lost the prognostic significance in HER2 BC.

Loi and colleagues conducted a pooled analysis included 2148 patients of 9 studies to evaluate the value of stromal TILs in early–TNBC. The authors demonstrated that every 10% increase in TILs revealed significant improvement in invasive disease–free survival (iDFS) 0.87 (95% CI, 0.83–0.91), distant disease–free survival (D–DFS) 0.83 (95% CI, 0.79–0.88) and OS 0.84 (95% CI 0.79–0.89)[22]. In another pooled analysis included 991 TNBC patients with lymph node negative, TLIs ≥20% had 5–year DFS (92% CI: 87–97%)[30].

Moreover, there are data about the effect of metronomic chemotherapy on the immune system, and the possibility of using TILs as a predictive marker in TNBC patients treated with metronomic chemotherapy in the maintenance setting.

Referring to the previous data, Further studies are needed to implement TILs as a standard biomarker for response to NAC in TNBC patients.

Limitations

The study was retrospective with a small sample size. The data collection depended mainly on medical documentation. Also, treatment selections varied among the main responsible physicians. So the results might be subjected to selection bias.

Conclusion

Our results reveal that a high pre–treatment level of TILs was a worthy predictor for response to NAC and could give us beneficial information on prognosis in TNBC. The

realization of our results requires a large, well–planned and prospective study.

Disclosure

The authors certify that there is no potential or actual conflict of interest related to this research.

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