International Journal of
Life Sciences
International Peer Reviewed Open Access Refereed Journal

Int. J. of Life Sciences, 2018; 6 (3):719-732
ISSN:2320-7817(p) | 2320-964X(o)

Original Article Open Access

Prognostic Value of Percentage of Positive to Total Excised Axillary Lymph Nodes in Egypt with Triple Negative Breast Cancer: Multiple-Centers Experience

Mansour M Morsy[1], Ahmed Raafat[1*], Abd el Motaleb Mohamed[2] , Alaa Fayed[2] and Mohamed Farouk Amin[1]

[1]Surgery department, Faculty of Medicine, Zagazig University Hospitals. Zagazig, Egypt.
[2]Clinical Oncology department, Faculty of Medicine, Zagazig University Hospitals. Zagazig, Egypt.
*Correspnding Author : Ahmed Raafat, MD, Surgery department, Faculty of Medicine, Zagazig University Hospitals. Zagazig, Egypt. / Email:ahmedraafat@yahoo.com

Manuscript details:

Received : 03.08.2018
Revised : 26.08.2018
Accepted : 03.09.2018
Published : 20.09.2018

Editor: Dr. Arvind Chavhan

Cite this article as:
Mansour M Morsy, Ahmed Raafat, Abd el Motaleb Mohamed, Alaa Fayed and Mohamed Farouk Amin (2018) Prognostic Value of Percentage of Positive to Total Excised Axillary Lymph Nodes in Egypt with Triple Negative Breast Cancer: Multiple-Centers Experience, *Int. J. of. Life Sciences*, Volume 6(3): 719-732.

Available online on http://www.ijlsci.in
ISSN: 2320-964X (Online)
ISSN: 2320-7817 (Print)

ABSTRACT

Background: The total number of axillary lymph nodes [LNs] is the most important prognostic factor in breast cancer. Over long times, different studies indicated that the lymph node ratio [LNR] might predict outcome better than the number of positive LNs. The aim of this retrospective study was to evaluate prognostic value of the lymph node ratio [LNR] in triple negative breast cancer [TNBC].

Materials and Methods: sixety patients with triple negative breast cancer [TNBC] at Zagazig University Hospitals and Fakous Cancer Center were included. We analyzed the impact lymph node ratio [LNR] on the disease free survival [DFS] and overall survival [OS] [calculated by Kaplan–Meier method].

Results: our results showed that the optimal cut off value of LNR value was 0.65, and the optimal cut off value of PLN. The Kaplan–Meier survival analysis showed the higher value of Mean disease free survival among all patients was 33.21 months and 3 year DFS was 50.6%. Disease free survival was significantly longer in those with LNR ≤ 0.65 than those with LNR > 0.65 [Mean: 33.34 months versus 27.46 months; 3year DFS 56.4% versus 36.9% respectively]. Mean overall survival among all patients was 36.90 months and 3 year OS was 50.4%. Overall survival was significantly longer in those with LNR ≤ 0.65 than those with LNR > 0.65 [Mean: 39.40 months versus 29.63 months; 3 year OS 73.8% versus 23.3% respectively].

Conclusion: These results suggest that TNBC patients with lower value of LNR good prognosis than with high LNR patients. The LNR is an independent prognostic factor, thus, LNR may be added to the current staging system.

Key Words: Triple-negative Breast cancer [TNBC], Lymph node ratio, Axillary lymph node,

INTRODUCTION

Breast carcinoma is the most common cancer among females accounting for 37.7% of their total malignancies in Egypt (Fernando et al., 2011) Triple-negative breast cancer [TNBC] is aggressive sub-group of breast cancers with negative estrogen receptors [ER], progesterone receptors [PR] or human epidermal growth factor receptor 2 [HER2](Fulford et al., 2007) The additional markers for cytokeratin 5/6 and epidermal growth factor receptor divide TNBC into 'basal-like' [BBC] and 'normal-like' sub-types. BBC is a particularly aggressive sub-type defined by genes expressed by epithelial cells in the basal layer of the adult mammary gland (Dogan & Turnbull, 2012).

Moreover, it is the leading cause of cancer related mortality in Egypt, constituting about 29.1% of all cancer related mortality (Fernando et al., 2011) The triple negative breast cancer [TNBC] represented 15% of invasive breast cancers .The TNM staging system had been used for classify patients into comparable groups and modifies the management options (Chen et al., 2010). In the current TNM classification [7th edition] of the American Joint Committee on Cancer [AJCC], the nodal status of breast cancer is mainly depended on the absolute number of involved LNs (Rizzo et al., 2009). An increase in the number of positive LNs is independently associated with decrease in overall survival , regardless of tumor size (Coleman et al., 2008). Moreover, the loco-regional recurrence risk is increased with a growing number of involved LNs (Zhu & Wu, 2012).

The total number of positive axillary lymph nodes [LNs] is the most important prognostic factor in breast cancer (Vinh-Hung et al., 2003). The TNM classification does not account for the total number of LNs removed. There is disagreement on the extent of the axillary lymph node dissection [ALND]. An inadequate ALND might lead to under staging of the axilla. The AJCC recommends at least 6 LNs to be removed and examined, but in general it is accepted that at least 10 LNs should be removed to accurately stage the axilla (Lale Atahan et al., 2008).

In the last decade, several authors have suggested that the lymph node ratio [LNR], defined as the ratio of positive LNs to the total number of removed LNs, is a prognostic factor in breast cancer (Ahn et al., 2011). In many studies, LNR is even considered more important than the absolute number of positive axillary LNs [11]. Some authors suggest LNR should be considered as an alternative to pN staging (Wang et al., 2012). The prognostic value of the LNR has already been demonstrated for other malignancies, including colorectal cancer (Liao et al., 2015).

Many studies regarding LNR in breast cancer demonstrated a large variation in the cutoff points used to classify patients in risk categories according to their LNR (Tausch et al., 2012).Some authors divided the patients into 2 LNR risk groups, whereas others established 3 LNR risk groups (Chen et al., 2015). In a big study conducting a boot strap sampling method and analyzed data of 1,829 node positive breast cancer patients, based on maximum likelihood, they classified patients into low-risk [<0.20], intermediate-risk [0.21–0.65], and high-risk [>0.65] LNR groups (Kim et al., 2013).

Many studies have proposed that LNR may be an alternative staging system for prognosis because they observed that the LNR system predicted prognosis better than the traditional LNP system [using pN1–3 classification is a categorization of the LNP system.[4–6]. Patients with Stage III TNBC breast cancer are represented nearly 6–7% of all invasive breast cancer patients per year in the world (Kim et al., 2011) and subgroup Stage IIIC had the worst prognostic stage in Stage III ((Vinh-Hung et al., 2009a and Vinh-Hung et al., 2009b).

In especial study the patients with more than 4 LNS could LNR have a prognostic value over pN , the different prognostic factors is determined including gender, tumor size, histopathological data , hormonal receptors , and management protocols ((Vinh-Hung et al., 2010a).now days studies evaluating the effect of LNR on overall survival [OS] and disease-free survival [DFS] in patients with pN3((Kim et al., 2011, Vinh-Hung et al., 2009a and Vinh-Hung et al., 2009b) .The high rate of recurrence and death were two characteristics of Stage III breast cancer ((Vinh-Hung et al., 2009b).

The aim of this work was analyze clinico-pathological characteristics and prognostic effect LNR for the TNBC patients in Egypt . The cut-off value was 0.65 to stratify the patients into different subgroups according to LNR.

MATERIALS AND METHODS

This retrospective study included the breast cancer proved pathologically, between March 2013 and

November 2017. All patients' information collected from the hospital-based cancer registry files of the department of Clinical Oncology Zagazig University and Fakous Cancer Center.

The breast cancer patients with invasive non-metastatic breast cancer underwent axillary lymph node dissection in conservative surgery or modified radical mastectomy. No previous neo-adjuvant chemotherapy, not inflammatory breast cancer. This research protocol for this study was approved by the Ethics Committees and informed consent at the Clinical Oncology department Zagazig University and Fakous Cancer Center

The Lymph Node Ratio [LNR] was calculated as the total number of PLNs to the total number of lymph nodes dissected, and the PLN was calculated as the total number of PLNs. Overall survival [OS] was estimated from date of diagnosis to date of last follow-up or death from breast cancer. Disease free survival [DFS] was defined as the time between date of surgery and date of last follow-up or date of best available evidence of the first unfavorable event: local recurrence, metastases, or death. Loco-regional recurrence was defined as any recurrence in the ipsilateral chest wall, or lymph node.

Statistical Analysis

Continuous variables were expressed as the mean ± SD & median [range], and the categorical variables were expressed as a number [percentage]. Continuous variables were checked for normality by using Shapiro-Wilk test. Independent samples Student's t-test was used to compare between two groups of normally distributed variables, while Mann Whitney U test was used for non-normally distributed variables. Percent of categorical variables were compared using Pearson's Chi-square test or Fisher's exact test when was appropriate. Trend of change in distribution of relative frequencies between ordinal data were compared using Chi-square test for trend. Disease Free Survival [DFS] was calculated as the time from surgery to relapse or the most recent workup in which patient was free from relapse [censored]. Overall Survival [OS] was calculated as the time from diagnosis to death or the most recent follow-up contact [censored]. Stratification of DFS and OS was done according LNRC. These time-to-event distributions were estimated using the method of Kaplan-Meier plot, and compared using two-sided exact log-rank test. All tests were two sided. A p-value <0.05 was considered significant. All statistics were performed using SPSS 22.0 for windows [SPSS Inc., Chicago, IL, USA] and MedCalc windows [MedCalc Software bvba 13, Ostend, Belgium].

RESULTS

Clinopathological parameters, LNR & LNRC, Treatment and Outcome

The current study included 60 triple negative breast cancer patients with mean age of 43.25 years and range 23 – 62 years, 27 patients [45%] were 20-40 years and 33 patients [55%] were 41-60 years, 29 patients [48.3%] were premenopausal, 31 patients [51.7%] had left breast cancer, 28 patients [46.7%] had grade II tumors while 32 patients [53.3%] had grade III tumors. Four patients [6.7%] had T1 tumors, 29 patients [48.3%] had T2 tumors, 25 patients [41.7%] had T3 tumors and only two patients [3.3%] had T4 tumors. Patients had 1-3 positive lymph nodes [N1] were three patients [5%], patients had 4-9 positive lymph nodes [N2] were 25 patients [41.7%], and patients had >9 positive lymph nodes [N3] were 32 patients [53.3%]. Minimum resected lymph nodes were 8 lymph nodes while maximum resected lymph nodes were 30 lymph nodes with median 16 lymph nodes. Minimum negative lymph nodes were 0 lymph nodes while maximum negative lymph nodes were 17 lymph nodes with median 7 lymph nodes. Minimum positive lymph nodes were 2 lymph nodes while maximum positive lymph nodes were 15 lymph nodes with median 10 lymph nodes. Mean lymph node ratio [LNR] was 0.56 and range 0.15 – 1.00, 40 patients [66.7%] had LNR≤0.65 while 20 patients had LNR>0.65.

All the studied patients received chemotherapy and radiotherapy, non-platinum regimen were received in 47 patients [78.3%] include FAC in 13.3%, FEC100 in 15%, AC-Taxol in 28.3%, AC-Taxotere in 8.3%, EC-Taxotere in 8.3%, FEC-Taxotere in 5% while platinum regimen were received in 13 patients [21.7%] in form of AC-TC protocol. Median follow-up was 23.66 months. Relapse had occurred in 22 patients [36.7%], local recurrence had occurred in 11 patients [18.3%], bone metastasis had occurred 9 patients [15%], liver metastasis had occurred in 12 patients [20%], lung metastasis had occurred in 10 patients [16.7%] and brain metastasis had occurred in 7 patients [11.7%]. By the end of follow-up 13 patients [21.7%] were died. Table [1]

Table 1: Clinopathological parameters, LNRC and outcome of triple negative breast cancer patients [N=60].

Characteristics	All studied patients [N=60] No.	%	Characteristics	All studied patients [N=60] No.	%
Age [year]			Chemotherapy protocol		
Mean ± SD	43.25	±12.02	FAC	8	13.3%
Median [range]	47	[23 – 62]	FEC100	9	15%
20-40 years	27	45%	AC-Taxol	17	28.3%
41-60 years	33	55%	AC-Taxotere	5	8.3%
Menopausal			EC-Taoxtree	5	8.3%
Premenopausal	29	48.3%	AC-TC	13	21.7%
Postmenopusal	31	51.7%	FEC-Taxotere	3	5%
Side			Regimen		
Right breast	29	48.3%	Non-platinum	47	78.3%
Left breast	31	51.7%	Platinum	13	21.7%
Grade			Follow-up [month]		
Grade II	28	46.7%	Mean ± SD	23.42	±7.55
Grade III	32	53.3%	Median [range]	23.66	[7.17 – 47.46]
T			Relapse		
T1	4	6.7%	Absent	38	63.3%
T2	29	48.3%	Present	22	36.7%
T3	25	41.7%	Local recurrence		
T4	2	3.3%	Absent	49	81.7%
N			Present	11	18.3%
N1	3	5%	Bone metastasis		
N2	25	41.7%	Absent	51	85%
N3	32	53.3%	Present	9	15%
RLNs			Liver metastasis		
Mean ± SD	16.96	±3.83	Absent	48	80%
Median [range]	16	[8 – 30]	Present	12	20%
NLNs			Lung metastasis		
Mean ± SD	7.53	±3.36	Absent	50	83.3%
Median [range]	7	[0 – 17]	Present	10	16.7%
PLNs			Brain metastasis		
Mean ± SD	9.43	±3.06	Absent	53	88.3%
Median [range]	10	[2 – 15]	Present	7	11.7%
LNR			Mortality		
Mean ± SD	0.56	±0.16	Alive	47	78.3%
Median [range]	0.58	[0.15 – 1.00]	Died	13	21.7%
LNRC					
≤0.65	40	66.7%			
>0.65	20	33.3%			

Continuous variables were expressed as mean ± SD & median [range]; categorical variables were expressed as number [percentage];

Relation between clinopathological parameters and LNRC

Mean age of triple negative patients with LNR≤0.65 was significantly older than those with LNR>0.65 [46.50 vs 38.55 years respectively, p=0.027], also 78.8% of those with age 41-60 years had LNR≤0.65 versus 51.9% of those with age 20-40 years [p=0.028]. Among postmenopausal, 80.6% had LNR≤0.65 versus 51.7% among premenopausal [p=0.018]. Of left side patients 38.7% had LNR>0.65 versus 27.6% of right side patients

[p=0.361]. Among grade III tumors 40.6% had LNR>0.65 versus 25% of grade II tumors [p=0.200]. No patients with T4 tumors had LNR>0.65 versus 52% among T3 tumors, 20.7% among T2 tumors and 25% among T1 tumors [p=0.135]. 50% of N3 had LNR>0.65 versus 16% among N2 and 0% among N1 [p=0.004]. Mean RLNs of triple negative patients with LNR≤0.65 was insignificantly numerous than those with LNR>0.65 [17.50 vs 15.90 lymph node respectively, p=0.221]. Mean NLNs of triple negative patients with LNR≤0.65 was significantly numerous than those with LNR>0.65 [9.02 vs 4.55 lymph node respectively, p<0.001]. Mean PLNs of triple negative patients with LNR≤0.65 was significantly fewer than those with LNR>0.65 [8.47 vs 11.35 lymph node respectively, p<0.001]. Mean LNR among those with LNR≤0.65 was 0.47 versus 0.72 among LNR>0.65. **Table [2]**

Table 2: Relation between clinopathological parameters and LNRC in triple negative breast cancer patients.

Characteristics	N	LNRC ≤0.65 [N=40] No.	[%]	LNRC >0.65 [N=20] No.	[%]	p-value
Age [year]						
Mean ± SD		46.50	±11.43	38.55	±12.07	0.027•
Median [range]		50	[25 – 62]	36	[23 – 60]	
20-40 years	27	14	[51.9%]	13	[48.1%]	0.028‡
41-60 years	33	26	[78.8%]	7	[21.2%]	
Menopausal						
Premenopausal	29	15	[51.7%]	14	[48.3%]	0.018‡
Postmenopusal	31	25	[80.6%]	6	[19.4%]	
Side						
Right breast	29	21	[72.4%]	8	[27.6%]	0.361‡
Left breast	31	19	[61.3%]	12	[38.7%]	
Grade						
Grade II	28	21	[75%]	7	[25%]	0.200‡
Grade III	32	19	[59.4%]	13	[40.6%]	
T						
T1	4	3	[75%]	1	[25%]	0.135§
T2	29	23	[79.3%]	6	[20.7%]	
T3	25	12	[48%]	13	[52%]	
T4	2	2	[100%]	0	[0%]	
N						
N1	3	3	[100%]	0	[0%]	0.004§
N2	25	21	[84%]	4	[16%]	
N3	32	16	[50%]	16	[50%]	
RLNs						
Mean ± SD		17.50	±4.20	15.90	±2.77	0.221•
Median [range]		17	[10 – 30]	16	[8 – 22]	
NLNs						
Mean ± SD		9.02	±3.04	4.55	±1.43	<0.001•
Median [range]		8	[6 – 17]	5	[0 – 7]	
PLNs						
Mean ± SD		8.47	±3.19	11.35	±1.56	<0.001*
Median [range]		8.50	[2 – 15]	12	[8 – 15]	
LNR						
Mean ± SD		0.47	±0.13	0.72	±0.07	<0.001*
Median [range]		0.50	[0.15 – 0.65]	0.70	[0.67 – 1.00]	

Continuous variables were expressed as mean ± SD & median [range]; categorical variables were expressed as number [percentage]; * Independent samples Student's t-test; • Mann Whitney U test; ‡ Chi-square test; § Chi-square test for trend; p<0.05 is significant.

Table 3: Relation between LNRC and chemotherapy protocol in triple negative breast cancer patients.

	LNRC				p-value‡
	≤0.65 [N=40]		>0.65 [N=20]		
Chemotherapy	No.	[%]	No.	[%]	
Protocol					
FAC	5	[12.5%]	3	[15%]	0.475
FEC100	6	[15%]	3	[15%]	
AC-Taxol	9	[22.5%]	8	[40%]	
AC-Taxotere	3	[7.5%]	2	[10%]	
EC-Taoxtree	3	[7.5%]	2	[10%]	
AC-TC	12	[30%]	1	[5%]	
FEC-Taxotere	2	[5%]	1	[5%]	
Regimen					
Non-platinum	28	[70%]	19	[95%]	0.043
Platinum	12	[30%]	1	[5%]	

Categorical variables were expressed as number [percentage]; ‡ Chi-square test; p<0.05 is significant.

Table 4: Effect of LNRC on outcome in triple negative breast cancer patients.

	LNRC				p-value‡
	≤0.65 [N=40]		>0.65 [N=20]		
Outcome	No.	[%]	No.	[%]	
Relapse					
Absent	29	[72.5%]	9	[45%]	0.037
Present	11	[27.5%]	11	[55%]	
Local recurrence					
Absent	36	[90%]	13	[65%]	0.031
Present	4	[10%]	7	[35%]	
Bone metastasis					
Absent	35	[87.5%]	16	[80%]	0.464
Present	5	[12.5%]	4	[20%]	
Liver metastasis					
Absent	34	[85%]	14	[70%]	0.189
Present	6	[15%]	6	[30%]	
Lung metastasis					
Absent	37	[92.5%]	13	[65%]	0.012
Present	3	[7.5%]	7	[35%]	
Brain metastasis					
Absent	39	[97.5%]	14	[70%]	0.004
Present	1	[2.5%]	6	[30%]	
Mortality					
Alive	37	[92.5%]	10	[50%]	<0.001
Died	3	[7.5%]	10	[50%]	

Categorical variables were expressed as number [percentage]; ‡ Chi-square test; p<0.05 is significant.

Relation between LNRC and chemotherapy protocol

70% of triple negative patients with LNR≤0.65 received non-platinum regimen versus 95% among triple negative patients with LNR≤0.65 [p=0.043]. 30% of triple negative patients with LNR≤0.65 had received AC-TC versus 5% among triple negative patients with LNR≤0.65. Table [3].

Effect of LNRC on outcome

27.5% of triple negative patients with LNR≤0.65 relapsed versus 55% of those with LNR>0.65 [p=0.037]. Local recurrence occurred more frequently in those with LNR>0.65 than those with LNR≤0.65 [35% vs 10% respectively, p=0.031]. Bone and liver metastasis occurred nearly equal in both groups while lung and brain metastasis occurred more frequently in those with

LNR>0.65 than those with LNR≤0.65. Regarding mortality, 50% of those with LNR>0.65 had died versus 7.5% among those with LNR≤0.65 [p<0.001]. Table [4].

Effect of LNRC on survival

Mean disease free survival among all patients was 33.21 months and 3 year DFS was 50.6%. Disease free survival was significantly longer in those with LNR≤0.65 than those with LNR>0.65 [Mean: 33.34 months versus 27.46 months; 3year DFS 56.4% versus 36.9% respectively]. Mean overall survival among all patients was 36.90 months and 3 year OS was 50.4%. Overall survival was significantly longer in those with LNR≤0.65 than those with LNR>0.65 [Mean: 39.40 months versus 29.63 months; 3year OS 73.8% versus 23.3% respectively]. Table [5] & Figure [1 A, B, D & E].

Table 5: Effect of LNRC on survival in triple negative breast cancer patients [N=60].

Survival	All patients [N=60]	LNRC ≤0.65 [N=40]	LNRC >0.65 [N=20]	p-value†
DFS				
Mean [month]	33.21 month	33.34 month	27.46 month	0.020
[95%CI]	[28.72 – 37.70]	[28.84 – 37.85]	[19.85 – 35.06]	
Median DFS	NR	NR	19.77 month	
1 year DFS [%]	91.5%	100%	75%	
2 year DFS [%]	61.1%	67.9%	46.2%	
3 year DFS [%]	50.6%	56.4%	36.9%	
OS				
Mean [month]	36.90 month	39.40 month	29.63 month	<0.001
[95%CI]	[32.26 – 41.53]	[35.56 – 43.24]	[23.74 – 35.53]	
Median OS	NR	NR	27.20 month	
1 year OS [%]	100%	100%	100%	
2 year OS [%]	83.5%	92.3%	67.4%	
3 year OS [%]	50.4%	73.8%	23.3%	

Continuous variables were expressed as mean [95%CI] & Median; Categorical variables were expressed as number [percentage]; 95%CI: 95% Confidence Interval; NR: not reached yet; † Log rank test; p<0.05 is significant.

Table 6: Effect of chemotherapy on survival in triple negative breast cancer patients [N=60].

Survival	All patients [N=60]	Chemotherapy regimen Non-platinum [N=47]	Chemotherapy regimen Platinum [N=13]	p-value†
DFS				
Mean [month]	33.21 month	33.88 month	28.61 month	0.461
[95%CI]	[28.72 – 37.70]	[28.92 – 38.83]	[19.73 – 37.49]	
Median DFS	NR	NR	24 month	
1 year DFS [%]	91.5%	89.4%	100%	
2 year DFS [%]	61.1%	65.5%	41.3%	
3 year DFS [%]	50.6%	52.8%	42.3%	
OS				
Mean [month]	36.90 month	35.68 month	40.15 month	0.439
[95%CI]	[32.26 – 41.53]	[30.47 – 40.89]	[34.85 – 45.45]	
Median OS	NR	33.40 month	NR	
1 year OS [%]	100%	100%	100%	
2 year OS [%]	83.5%	83%	90%	
3 year OS [%]	50.4%	42.8%	90%	

Continuous variables were expressed as mean [95%CI] & Median; Categorical variables were expressed as number [percentage]; 95%CI: 95% Confidence Interval; NR: not reached yet; † Log rank test; p<0.05 is significant.

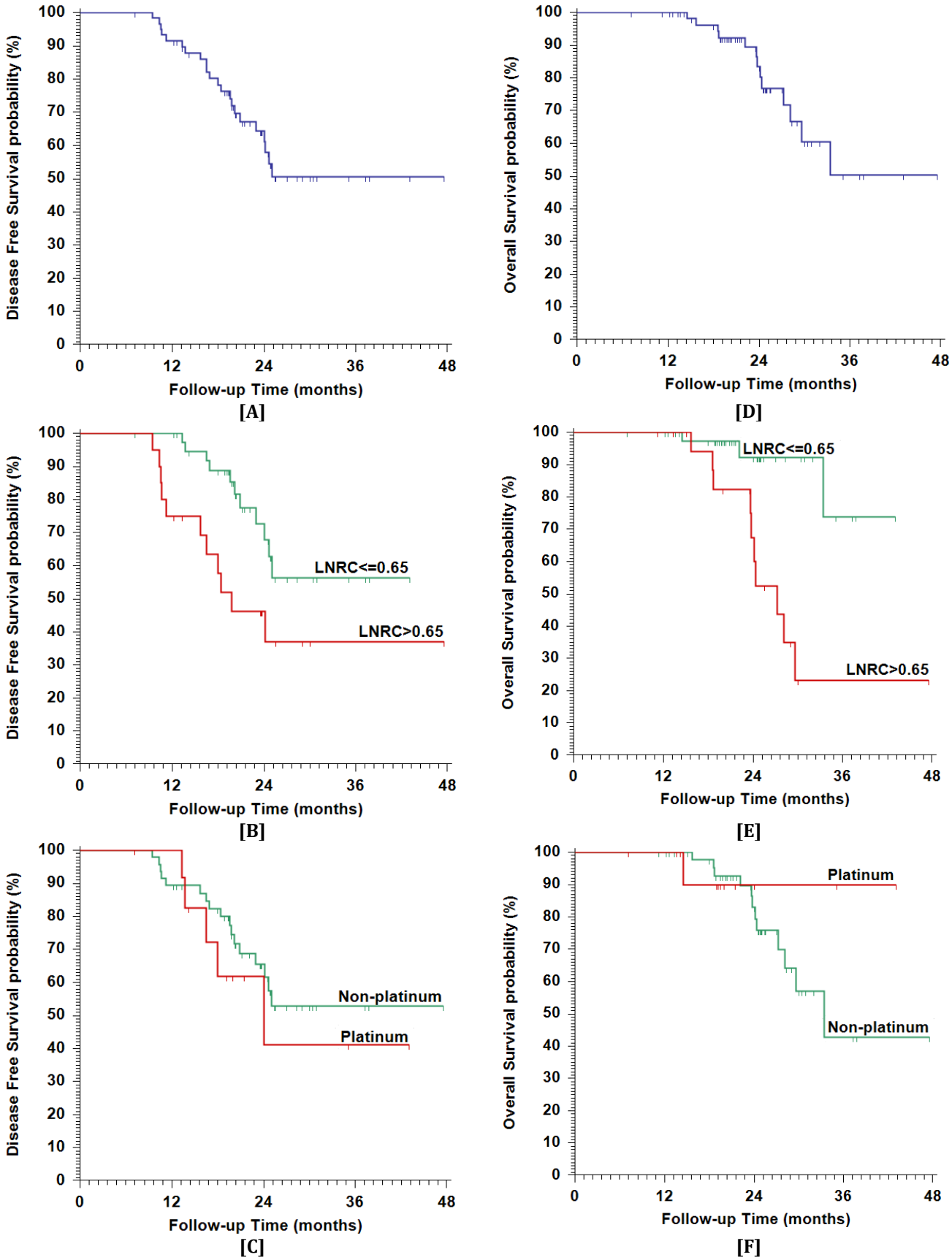

Figure 1: Kaplan Meir plot of Disease Free Survival [Left panel] and Overall Survival [Right panel]: [A] & [D] all studied patients, [B] & [E] stratified by LNRC, [C] & [F] stratified by chemotherapy regimen.

Effect of chemotherapy on survival

Disease free survival was insignificantly longer in those received non-platinum regimen than received platinum regimen [Mean: 33.88 months versus 28.61 months; 3year DFS 52.8% versus 42.3% respectively]. Overall survival was insignificantly longer in those received platinum regimen than received non-platinum regimen [Mean: 40.15 months versus 35.68 months; 3year OS 90% versus 42.8% respectively]. Table [6] & Figure [1 C & F].

Effect of LNRC on survival among patients received non-platinum based regimen

Disease free survival was significantly longer in those with LNR≤0.65 than those with LNR>0.65 [Mean: 31.43 months versus 28.09 months; 3year DFS 59.7% versus 39.3% respectively]. Overall survival was significantly longer in those with LNR≤0.65 than those with LNR>0.65 [Mean: 35.46 months versus 29.47 months; 3year OS 62.8% versus 23% respectively]. Table [7] & Figure [2].

Table 7: Effect of LNRC on survival in triple negative breast cancer patients received non-platinum based regimen [N=47].

Survival	All patients [N=47]	LNRC ≤0.65 [N=28]	LNRC >0.65 [N=19]	p-value†
DFS				
Mean [month]	33.88 month	31.43 month	28.09 month	0.022
[95%CI]	[28.92 – 38.83]	[27.68 – 35.18]	[20.12 – 36.05]	
Median DFS	NR	NR	19.77 month	
1 year DFS [%]	89.4%	100%	73.7%	
2 year DFS [%]	65.5%	75%	49.1%	
3 year DFS [%]	52.8%	59.7%	39.3%	
OS				
Mean [month]	35.68 month	35.46 month	29.47 month	0.001
[95%CI]	[30.47 – 40.89]	[32.77 – 38.14]	[23.57 – 35.37]	
Median OS	33.40 month	NR	27.20 month	
1 year OS [%]	100%	100%	100%	
2 year OS [%]	83%	94.1%	66.5%	
3 year OS [%]	42.8%	62.8%	23%	

Continuous variables were expressed as mean [95%CI] & Median; Categorical variables were expressed as number [percentage]; 95%CI: 95% Confidence Interval; NR: not reached yet; † Log rank test; p<0.05 is significant.

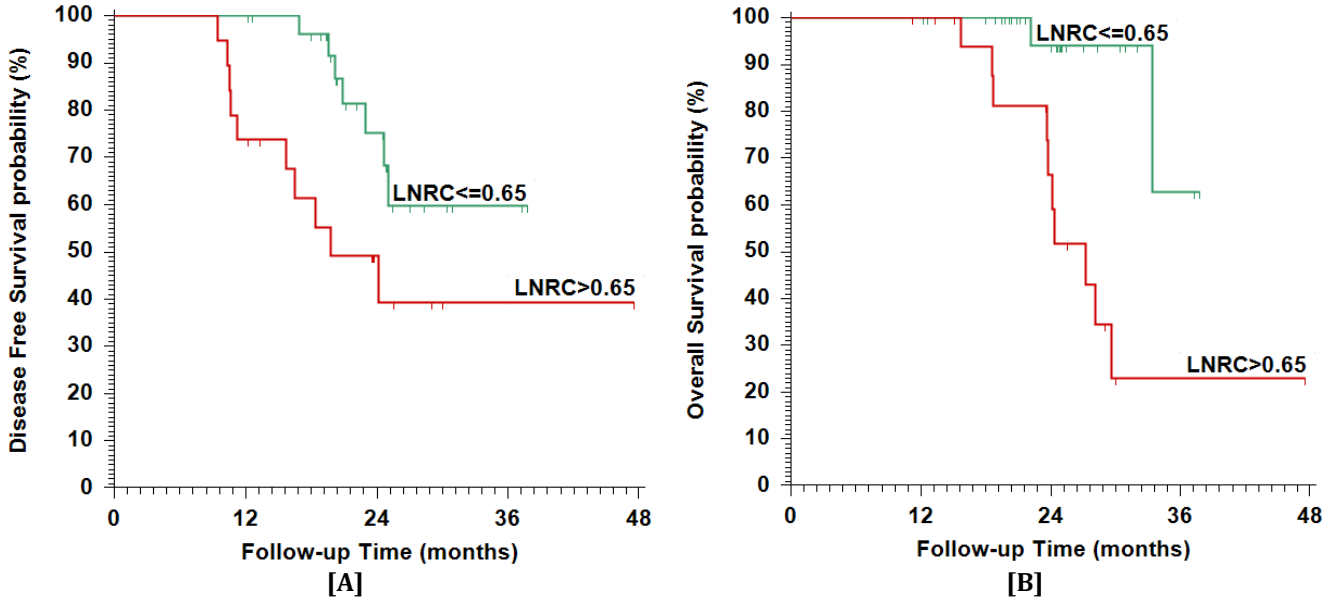

Figure 2: Kaplan Meir plot of Disease Free Survival [Left panel] and Overall Survival [Right panel] stratified by LNRC among triple negative breast cancer patients received non-platinum based regimen [N=47].

Effect of clinopathological parameters and treatment on relapse

Mean age of patients free from relapse was insignificantly older than those with relapse [44.21 vs 41.59 years respectively, p=0.565], also 69.7% of those with age 41-60 years had no relapse versus 55.6% of those with age 20-40 years [p=0.258]. Among postmenopausal, 29% had relapse versus 44.8% among premenopausal [p=0.205]. Of left side patients 41.9% had relapse versus 31% of right side patients [p=0.381]. Among grade III tumors 43.8% had relapse versus 28.6% of grade II tumors [p=0.224]. 100% patients with T4 tumors had relapse versus 44% among T3 tumors, 27.6 among T2 tumors and 25% among T1 tumors [p=0.054]. 40.6% of N3 had relapse versus 32% among N2 and 33.3% among N1 [p=0.539]. Mean RLNs of patients free from relapse was insignificantly fewer than those with relapse [16.47 vs 17.81 lymph node respectively, p=0.473]. Mean NLNs of patients free from relapse was insignificantly numerous than those relapse [7.57 vs 7.45 lymph node respectively, p=0.491]. Mean PLNs of patients free from relapse was insignificantly fewer than those with relapse [8.89 vs 10.36 lymph node respectively, p=0.068]. Mean LNR of patients free from relapse was insignificantly fewer than those with relapse [0.54 vs 0.58 respectively, p=0.158]. Among patients with LNR>0.65, 55% had relapse versus 27.5% among patients with LNR≤0.65 [p=0.037]. Of patients received platinum regimen, 38.5% had relapse versus 36.2% of patients received non-platinum regimen [p=1.000]. Among patients received FAC, 12.5% had relapse versus 44.4% among patients received FEC100, 47.1% among patients received AC-Taxol, 0% among patients received AC-Taxotere, 60% among patients received EC-Taxotere, and 33.3% among patients received FEC-Taxore [p=0.308]. Table [8].

Table 8: Effect of clinopathological parameters and treatment on relapse in triple negative breast cancer patients.

	N	Relapse				p-value
		Absent [N=38]		Present [N=22]		
Parameters		No.	[%]	No.	[%]	
Age [year]						
Mean ± SD		44.21	±10.97	41.59	±13.75	0.565•
Median [range]		49	[23 – 62]	42.50	[24 – 60]	
20-40 years	27	15	[55.6%]	12	[44.4%]	0.258‡
41-60 years	33	23	[69.7%]	10	[30.3%]	
Menopausal						
Premenopausal	29	16	[55.2%]	13	[44.8%]	0.205‡
Postmenopusal	31	22	[71%]	9	[29%]	
Side						
Right breast	29	20	[69%]	9	[31%]	0.381‡
Left breast	31	18	[58.1%]	13	[41.9%]	
Grade						
Grade II	28	20	[71.4%]	8	[28.6%]	0.224‡
Grade III	32	18	[56.3%]	14	[43.8%]	
T						
T1	4	3	[75%]	1	[25%]	0.054§
T2	29	21	[72.4%]	8	[27.6%]	
T3	25	14	[56%]	11	[44%]	
T4	2	0	[0%]	2	[100%]	
N						
N1	3	2	[66.7%]	1	[33.3%]	0.539§
N2	25	17	[68%]	8	[32%]	
N3	32	19	[59.4%]	13	[40.6%]	
RLNs						
Mean ± SD		16.47	±3.51	17.81	±4.28	0.473•
Median [range]		16.50	[8 – 25]	16	[12 – 30]	

Continuous variables were expressed as mean ± SD & median [range]; categorical variables were expressed as number [percentage]; • Mann Whitney U test; ‡ Chi-square test; § Chi-square test for trend; p<0.05 is significant.

Table 8 continued…

Parameters	N	Relapse				p-value
		Absent [N=38]		Present [N=22]		
		No.	[%]	No.	[%]	
NLNs						
Mean ± SD		7.57	±3.30	7.45	±3.52	0.491•
Median [range]		7	[0 – 17]	6.50	[4 – 17]	
PLNs						
Mean ± SD		8.89	±2.98	10.36	±3.04	0.068•
Median [range]		9	[2 – 13]	11	[3 – 15]	
LNR						
Mean ± SD		0.54	±0.17	0.58	±0.15	0.158•
Median [range]		0.52	[0.15 – 1.00]	0.65	[0.25 – 0.75]	
LNRC						
≤0.65	40	29	[72.5%]	11	[27.5%]	0.037‡
>0.65	20	9	[45%]	11	[55%]	
Protocol						
FAC	8	7	[87.5%]	1	[12.5%]	0.308‡
FEC100	9	5	[55.6%]	4	[44.4%]	
AC-Taxol	17	9	[52.9%]	8	[47.1%]	
AC-Taxotere	5	5	[100%]	0	[0%]	
EC-Taoxtree	5	2	[40%]	3	[60%]	
AC-TC	13	8	[61.5%]	5	[38.5%]	
FEC-Taxotere	3	2	[66.7%]	1	[33.3%]	
Regimen						
Non-platinum	47	30	[63.8%]	17	[36.2%]	1.000‡
Platinum	13	8	[61.5%]	5	[38.5%]	

Continuous variables were expressed as mean ± SD & median [range]; categorical variables were expressed as number [percentage]; • Mann Whitney U test; ‡ Chi-square test; § Chi-square test for trend; $p<0.05$ is significant.

Effect of clinopathological parameters and treatment on mortality

Mean age of alive patients was significantly older than died patients [44.87 vs 37.38 years respectively, p=0.048], also 87.9% of those with age 41-60 years were alive versus 66.7% of those with age 20-40 years [p=0.047]. Among postmenopausal, 9.7% were died versus 34.5% among premenopausal [p=0.020]. Of left side patients 22.6% was died versus 20.7% of right side patients [p=0.859]. Among grade III tumors 25% was died versus 20.7% of grade II tumors [p=0.503]. 0% patients with T4 tumors were died versus 40% among T3 tumors, 10.3% among T2 tumors and 0% among T1 tumors [p=0.032]. 28.1% of N3 were died versus 16% among N2 and 0% among N1 [p=0.153]. Mean RLNs of alive patients was insignificantly fewer than died patients [16.72 vs 17.84 lymph node respectively, p=0.355]. Mean NLNs of alive patients was insignificantly numerous than died patients [7.82 vs 6.46 lymph node respectively, p=0.050]. Mean PLNs of alive patients was significantly fewer than died patients [8.89 vs 11.38 lymph node respectively, p=0.001]. Mean LNR of alive patients was significantly fewer than died patients [0.52 vs 0.67 respectively, p=0.005]. Among patients with LNR>0.65, 50% were died versus 7.5% among patients with LNR≤0.65 [p<0.001]. Of patients received platinum regimen, 7.7% were died versus 25.5% of patients received non-platinum regimen [p=0.262]. Among patients received FAC, 12.5% were died versus 33.3% among patients received FEC100, 23.5% among patients received AC-Taxol, 20% among patients received AC-Taxotere, 40% among patients received EC-Taxotere, and 33.3% among patients received FEC-Taxore [p=0.692]. Of patients with relapse, 45.5% were died versus 7.9% among patients free from relapse [p=0.002]. Table [9]

Table 9: Effect of clinopathological parameters, treatment and relapse on mortality in triple negative breast cancer patients.

Parameters	N	Mortality				p-value
		Alive [N=47]		Died [N=13]		
		No.	[%]	No.	[%]	
Age [year]						
Mean ± SD		44.87	±11.55	37.38	±12.32	0.048•
Median [range]		50	[23 – 62]	32	[24 – 60]	
20-40 years	27	18	[66.7%]	9	[33.3%]	0.047‡
41-60 years	33	29	[87.9%]	4	[12.1%]	
Menopausal						
Premenopausal	29	19	[65.5%]	10	[34.5%]	0.020‡
Postmenopusal	31	28	[90.3%]	3	[9.7%]	
Side						
Right breast	29	23	[79.3%]	6	[20.7%]	0.859‡
Left breast	31	24	[77.4%]	7	[22.6%]	
Grade						
Grade II	28	23	[82.1%]	5	[17.9%]	0.503‡
Grade III	32	24	[75%]	8	[25%]	
T						
T1	4	4	[100%]	0	[0%]	0.032§
T2	29	26	[89.7%]	3	[10.3%]	
T3	25	15	[60%]	10	[40%]	
T4	2	2	[100%]	0	[0%]	
N						
N1	3	3	[100%]	0	[0%]	0.153§
N2	25	21	[84%]	4	[16%]	
N3	32	23	[71.9%]	9	[28.1%]	
RLNs						
Mean ± SD		16.72	±3.31	17.84	±5.39	0.355*
Median [range]		16	[10 – 25]	17	[8 – 30]	
NLNs						
Mean ± SD		7.82	±3.08	6.46	±4.17	0.050•
Median [range]		7	[3 – 17]	5	[0 – 17]	
PLNs						
Mean ± SD		8.89	±3.15	11.38	±1.70	0.001*
Median [range]		9	[2 – 15]	12	[8 – 15]	
LNR						
Mean ± SD		0.52	±0.15	0.67	±0.13	0.005•
Median [range]		0.52	[0.15 – 0.80]	0.68	[0.43 – 1.00]	
LNRC						
≤0.65	40	37	[92.5%]	3	[7.5%]	<0.001‡
>0.65	20	10	[50%]	10	[50%]	
Protocol						
FAC	8	7	[87.5%]	1	[12.5%]	0.692‡
FEC100	9	6	[66.7%]	3	[33.3%]	
AC-Taxol	17	13	[76.5%]	4	[23.5%]	
AC-Taxotere	5	4	[80%]	1	[20%]	
EC-Taoxtree	5	3	[60%]	2	[40%]	
AC-TC	13	12	[92.3%]	1	[7.7%]	
FEC-Taxotere	3	2	[66.7%]	1	[33.3%]	

Continuous variables were expressed as mean ± SD & median [range]; categorical variables were expressed as number [percentage]; * Independent samples Student's t-test; • Mann Whitney U test; ‡ Chi-square test; § Chi-square test for trend; $p<0.05$ is significant.

Table 9: Continue…

Parameters	N	Relapse				p-value
		Absent [N=38]		Present [N=22]		
		No.	[%]	No.	[%]	
Regimen						
Non-platinum	47	35	[74.5%]	12	[25.5%]	0.262‡
Platinum	13	12	[92.3%]	1	[7.7%]	
Relapse						
Absent	38	35	[92.1%]	3	[7.9%]	0.002‡
Present	22	12	[54.5%]	10	[45.5%]	

Continuous variables were expressed as mean ± SD & median [range]; categorical variables were expressed as number [percentage]; * Independent samples Student's t-test; • Mann Whitney U test; ‡ Chi-square test; § Chi-square test for trend; p<0.05 is significant.

DISCUSSION

The triple negative breast cancer is very aggressive and worst prognosis sub-group that has not estrogen receptors [ER], progesterone receptors [PR] or HER2 (Kim et al., 2006, Fulford et al., 2007 and Vinh-Hung et al., 2010a). In our study, we evaluate prognostic effect of LNR and set ideal cut-off value of them to distinguish between patient subgroups and forwarding a new staging system including LNR.

Many studies have suggesting that the LNR maybe an alternative staging system for prognosis because the predicted that LNR is more prognostic factor than traditional TNM staging system (Vinh-Hung et al., 2010b).

The number of involved axillary lymph nodes [LNs] is considered the most important prognostic factor in breast cancer (Vinh-Hung et al., 2003). The TNM classification does not account for the total number of LNs removed. There is disagreement on the extent of the axillary lymph node dissection [ALND]. An inadequate ALND might lead to understating of the axilla. The AJCC recommends at least 6 LNs to be removed and examined, but in general it is accepted that at least 10 LNs should be removed to accurately stage the axilla (Lale Atahan et al., 2008).

The current study included 60 triple negative breast cancer patients with mean age of 43.25 years and range 23 – 62 years, 27 patients [45%] were 20-40 years and 33 patients [55%] were 41-60 years, 29 patients [48.3%] were premenopausal, 31 patients [51.7%] had left breast cancer, 28 patients [46.7%] had grade II tumors while 32 patients [53.3%] had grade III tumors. Four patients [6.7%] had T1 tumors, 29 patients [48.3%] had T2 tumors, 25 patients [41.7%] had T3 tumors and only two patients [3.3%] had T4 tumors. Patients had 1-3 positive lymph nodes [N1] were three patients [5%], patients had 4-9 positive lymph nodes [N2] were 25 patients [41.7%], and patients had >9 positive lymph nodes [N3] were 32 patients [53.3%]. Minimum resected lymph nodes were 8 lymph nodes while maximum resected lymph nodes were 30 lymph nodes with median 16 lymph nodes. The minimum positive lymph nodes were 2 lymph nodes while maximum positive lymph nodes were 15 lymph nodes with median 10 lymph nodes. Mean lymph node ratio [LNR] was 0.56 and range 0.15 – 1.00, 40 patients [66.7%] had LNR≤0.65 while 20 patients had LNR>0.65. Among patients with LNR>0.65, 55% had relapse versus 27.5% among patients with LNR≤0.65 [p=0.037].

The incidence of relapse in our study was more in LNR more than 0.65 with the following result , the 27.5% of triple negative patients with LNR≤0.65 relapsed versus 55% of those with LNR>0.65 [p=0.037]. Local recurrednce occurred more frequently in those with LNR>0.65 than those with LNR≤0.65 [35% vs 10% respectively, p=0.031].

In our study Overall survival was significantly longer in those with LNR≤0.65 than those with LNR>0.65 [Mean: 35.46 months versus 29.47 months; 3year OS 62.8% versus 23% respectively] and Mean disease free survival among all patients was 33.21 months and 3 year DFS was 50.6%. Disease free survival was significantly longer in those with LNR≤0.65 than those with LNR>0.65 [Mean: 33.34 months versus 27.46 months; 3year DFS 56.4% versus 36.9% respectively]. Mean overall survival among all patients was 36.90 months and 3 year OS was 50.4%. Overall survival was significantly longer in those with LNR≤0.65 than those

with LNR>0.65 [Mean: 39.40 months versus 29.63 months; 3year OS 73.8% versus 23.3% respectively].

In current study the overall survival was insignificantly longer in those received platinum regimen than received non-platinum regimen [Mean: 40.15 months versus 35.68 months; 3year OS 90% versus 42.8% respectively].

There was study showing both the absolute number of positive lymph nodes and the strong effect of OS by univariate analysis and the multivariate analysis, only the LNR remained an independent predictor of OS, with a 2.5-fold increased risk of death at LNR of P0.25 (Hatoum et al., 2010).

In our study, LNR together with ER negativity and tumor grade were the only factors that were affect the DFS in the multivariate analysis. Patients with high LNRs were associated with a hazard ratio of recurrence of 2.2 and 3.2, respectively as compared with those in the low risk category similar to our study .

REFERENCE

Ahn SH, Kim HJ, Lee JW, Gong GY, Noh DY, Yang JH, *et al.* (2011) Lymph node ratio and pN staging in patients with node-positive breast cancer: A report from the Korean breast cancer society. *Breast Cancer Res Treat*;130:507-15

Chen SB, Weng HR, Wang G, Zou XF, Liu DT, Chen YP, *et al.* (2015) Lymph node ratio-based staging system for esophageal squamous cell carcinoma. *World J Gastroenterol*;21:7514-21

Chen WQ, Zheng RS, Zhang SW, Zeng HM, Zou XN. (2014) The incidences and mortalities of major cancers in China, 2010. *Chin J Cancer* ;33:402-5

Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R,Capocaccia R, *et al.* (2008) Cancer survival in five continents: A worldwidepopulation-based study. *Lancet* Oncol ;9:730-56

Dogan B.E. & Turnbull L. W. (2012) Imaging of triple-negative breast cancer. *Annals of Oncolog,*23[Suppl. 6]: vi23–vi29,

Fernando LM ,Vector PS ,David SP.,et al; (2011) Tiple negative breast cancer in Hispanic patients., *Cancer* 117;3658-69

Fulford LG, Reis-Filho JS, Ryder K et al. (2007) Basal-like grade III invasive ductal carcinoma of the breast: patterns of metastasis and long-term survival. *Breast Cancer Res*;9: R4.

Hatoum HA, Jamali FR, El-Saghir NS, et al. (2010) Ratio between positive lymph nodes and total excised axillary lymph nodes as an independent prognostic factor for overall survival in patients with nonmetastatic lymph node-positive breast cancer. *Indian Surg Oncol* ;1:305–12.

Kim JY, Ryu MR, Choi BO, *et al*. (2011) The prognostic significance of the lymph node ratio in axillary lymph node positive breast cancer. *Journal of breast cancer*;14:204-12

Kim MJ, Ro JY, Ahn SH et al. (2006) Clinicopathologic significance of the basal-like subtype of breast cancer: a comparison with hormone receptor and Her2/neu-overexpressing phenotypes. *Hum Pathol*; 37: 1217–1226.

Kim SI, Cho SH, Lee JS, *et al*. (2013) Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes. *British journal of cancer*;109:1165-71

Lale Atahan I, Yildiz F, Ozyigit G, Sari S, Gurkaynak M, Selek U, *et al.* (2008) Percent positive axillary lymph node metastasis predicts survival in patients with non-metastatic breast cancer. *Acta Oncol* ;47:232-8

Liao GS, Chou YC, Golshan M, Hsu HM, Hong ZJ, Yu JC, *et al.* (2015) Prognostic value of the lymph node ratio in breast cancer subtypes. *Am J Surg*;210:749-54.

Rizzo M, Lund MJ, Mosunjac M, Bumpers H, Holmes L, O'Regan R, *et al.* (2009) Characteristics and treatment modalities for African American women diagnosed with stage III breast cancer. *Cancer* ;115:3009-15

Saxena N, Hartman M, Yip CH, Bhoo-Pathy N, Khin LW, Taib NA, *et al.* (2012) Does the axillary lymph node ratio have any added prognostic value over pN staging for South East Asian breast cancer patients? *PLoS One* ;7:e45809

Tausch C, Taucher S, Dubsky P, Seifert M, Reitsamer R, Kwasny W, *et al.* (2012) Prognostic value of number of removed lymph nodes, number of involved lymph nodes, and lymph node ratio in 7502 Group [ABCSG]. *Ann Surg Oncol*;19:1808-17

Tawfik R. ElKhodary, Mohamed A. Ebrahim, Elsayed E. Hatata and Nermeen A. Niazy. Prognostic value of lymph node ratio in node-positive Breast cancer in Egyptian patients. *Journal of the Egyptian National Cancer Institute Journal of the Egyptian National Cancer Institute* 26, 31–35.

Vinh-Hung V et al (2009) Lymph node ratio as an alternative topN staging in node-positive breast cancer. *J Clin Oncol*. 27[7]:1062–1068

Vinh-Hung V, Burzykowski T, Cserni G, Voordeckers M, Van De Steene J, Storme G. (2003) Functional form of the effect of the numbers of axillary nodes on survival in early breast cancer. *Int J Oncol* ;22: 697-704

Vinh-Hung V, Joseph SA, Coutty N, Ly BH, Vlastos G, NguyenNP. (2010) Age and axillary lymph node ratio in postmenopausal womenwith T1-T2 node positive breast cancer. *Oncologist*.;15:1050–62.

Vinh-Hung V, Nguyen NP, Cserni G, Truong P, Woodward W,Verkooijen HM, et al. (2009) Prognostic value of nodal ratios in nodepositivebreast cancer: a compiled update. *Future Oncol*.;5:1585–603.

Vinh-Hung V, Verkooijen HM, Fioretta G, Neyroud-Caspar I,Rapiti E, Vlastos G, et al. (2009) Lymph node ratio as an alternative to pN staging in node-positive breast cancer. *J Clin Oncol*.;27:1062–8.

Wang F, He W, Qiu H, Wang X, Guo G, Chen X, *et al.* (2012) Lymph node ratio and pN staging show different superiority as prognostic predictors depending on the number of lymph nodes dissected in Chinese patients with luminal A breast cancer. *Clin Breast Cancer* ;12:404-11

Zhu C, Wu XZ. Proposal of new classification for stage III breast cancer on the number and ratio of metastatic lymph nodes.*(2012) J Surg Oncol* ;106:696-702.