Al-Azhar International Medical Journal

Volume 4 | Issue 10 Article 40

2023
Section: Onco-surgery

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How to Cite This Article

Sheta, Ahmed Mohamed; Asar, Mohamed Mamdouh; and Abd-Elmonem, Ashraf Abd-Elhamid (2023) "Assessment of lymph nodes status post neoadjuvant chemotherapy using sentinel lymph nodes in locally advanced breast cancer," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 10, Article 40.
DOI: https://doi.org/10.58675/2682-339X.1979

ORIGINAL ARTICLE

Assessment of Lymph Nodes Status Post Neoadjuvant Chemotherapy Using Sentinel Lymph Nodes in Locally Advanced Breast Cancer

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Abstract

Background: **Cancer clinics all over the globe have begun using sentinel lymph node (SLN) biopsy (SLNB) for node-negative early breast cancer since its debut. A negative SLN indicates that 95%−100% of the other LNs in that axilla are also negative. To evaluate patent blue dye in S/lN biopsy and its consequences to identify the axillary level of lymph node involvement, we will analyze its function in post-neoadjuvant chemotherapy treatment of locally advanced breast carcinoma.**

Methods: **This is a prospective cohort research carried out on 20 female patients with LABC who received neoadjuvant chemotherapy and will complete their management by modified radical mastectomy or conservative breast surgery with sentinel LN assessment for 6 months. Patients underwent identification, detection of level of SLN, and assessment of SLN pathology by frozen section (FzS).**

Results: **Notable differences were found between among positive, negative and suspicious. Notable differences were found between ALND (axillary LN dissection) and SLNB (*P* value = 0.007). Notable differences were found between ALND and SLNB (*P* value = 0.006). Notable differences were found between stained and nonstained LNs (*P* value = 0.019).**

Conclusion: **SLN detection rate was 85%, ALND revealed 5 cases (25%) were positive and 2 cases (10%) were negative. SLNB revealed one case (5%) was positive and 12 cases (60%) were negative. SLN detection rate definitely rose with experience, suggesting the existence of a learning curve.**

Keywords: Breast cancer, Neoadjuvant chemotherapy, Sentinel lymph nodes

1. Introduction

Since 1977, when Cabanas first described the sentinel lymph node biopsy (SLNB) for penile carcinoma, the term 'sentinel lymph node' (SLN) which describes the lymph node that receives lymphatic drainage first from the location of the main tumour.[1]

Technetium-99 (99Tc) was first used in SLNB for melanoma in 1993. Giuliano demonstrated the efficacy of SLN in breast cancer in 1994 by injecting patent blue dye into breast tumours (2). The safety and efficacy of SLNB for checking axillary nodes for spread in women with small breast cancers was demonstrated by Veronesi in 2013.[2]

In an attempt to reduce tumour growth, tumour clinical stage, and/or improve the rate of breast-conserving surgery, neoadjuvant chemotherapy (NACT) is commonly given to patients with operable BCs today. There has been an increase in the pathological complete response (pCR) rate of axillary nodes in patients with lymph node-positive

Accepted 5 June 2023.
Available online 24 January 2024

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https://doi.org/10.58675/2682-339X.1979

(cN+) breast cancers who were originally treated with NACT (4), and this has helped to evaluate the impacts of systemic treatment and tumour response. It has also made it possible to down-stage the clinically positive axilla in extremely positive responses, leading to fewer deleterious therapies.[3]

Definitive breast surgery, followed by radiation treatment if necessary, should be performed after prior chemotherapy. Additionally, patients should be treated with hormone treatment and trastuzumab that is tailored to their tumor's biologic characteristics.[4]

The degree to which lymph nodes are involved, the size of the tumour, and the histopathological grade of the tumour all play a role in determining a patient's prognosis when dealing with breast cancer. Treatment in the form of (Axillary LN dissection) ALND level I and II is deemed optimal because ALN status is considered the greatest singular predictor of prognosis for axillary nodal involvement. However, it is linked to a number of problems, including the self-limiting complaints of numbness (70%), pain (33%), weakness (25%), swelling (24%), and rigidity (15%). These symptoms can cause significant disruption to everyday life in up to 39% of cases. Cancer clinics all over the globe have begun using SLNB for node-negative early breast cancer since its debut. A negative SLN indicates that 95%–100% of the other LNs in that axilla are also negative. So, individuals with negative axillae can prevent unnecessary ALND, lowering the risk of ALND-related morbidity.

To evaluate patent blue dye in SLNB and its consequences to identify the axillary level of SLN, we will analyse its function in the post-NACT treatment of locally advanced breast carcinoma.

2. Patients and methods

This is a prospective cohort research carried out at the General surgery and surgical oncology departments Al-Azhar Cairo university hospitals and the Surgical oncology department at Tanta cancer center on 20 female patients with LABC who received neoadjuvant chemotherapy and will complete their management by modified radical mastectomy or conservative breast surgery with sentinel LN assessment for 6 months.

Written consent was taken from patients before including them in the research, and approval was obtained from the ethical committee of the department of General Surgery, Faculty of Medicine, Al-Azhar University.

Exclusion criteria include tumour size (T1, T2) stage, inflammatory breast cancer, clinically positive axilla post neoadjuvant chemotherapy, prior breast or axillary surgery, pregnancy, and male breast cancer.

The enrolled patients were subjected to history taking: discovery of the lump, history of previous breast operations, history of previous breast complaints, family history of breast cancer, and history of allergy to dye.

Full Clinical examination, which includes general and local examinations.

2.1. Investigations includes

2.1.1. Laboratory investigations

Routine laboratory investigation.

2.1.2. Imaging studies

Bilateral sonomamography if age >35 years old, MRI breast, metastatic work up, chest X-ray, bone scan, CT with contrast chest, abdomen, pelvis, tumour markers and preoperative (Echo, ECG).

Core tissue Biopsy with biological studies (ER, PR, HER2, KI67) or open biopsy.

2.2. Operative

Executed in a supine position with the ipsilateral arm abducted to 90° on an arm board. Breasts are examined beforehand, and 5 cc of patent blue dye is injected 30 min before operation into two different areas (the peritumoral space and the subareolar space). Fig. 1 shows the dual site injection (peritumoral & subareolar).

All clinically weakly localised tumours were identified by a needle under U/S or mammographic guidance, the tiny incision for SLNB detection of SLN, and breast massage following dye insertion. Fig. 2 shows the U/S guided marking of clinically undiagnosed mass, and Fig. 3 shows the small incision for SLN biopsy.

Fig. 1. Dual site injection (peritumoral and subareolar).

Fig. 2. U/S guided marking of clinically undiagnosed mass.

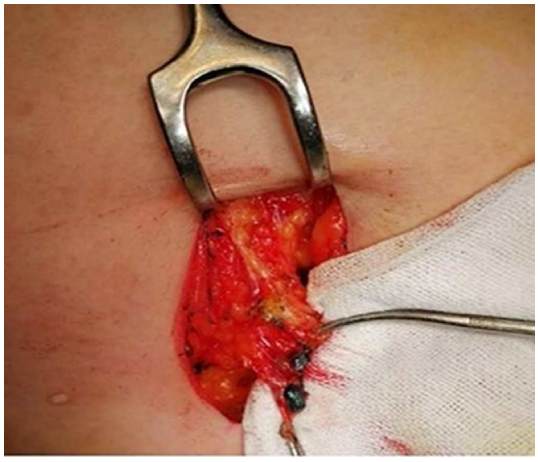

Fig. 3. Small incision for SLN biopsy.

Evaluation of SLN pathology by frozen section (FzS), dissection of axillary LNs if SLN positive then removal of breast mass by wide local excision along with conservative breast surgery, mammoplasty, or mastectomy based on mass to breast size, and eventually putting a drain with good hemostasis and wound closure. Fig. 4 shows the stained SLNs removed for the frozen section. Fig. 5 shows the marking and skin elliptical incision for lumpectomy.

2.3. After the procedure

Two- or three-day hospital stays, early limb mobilization, wound care, drain color and amount assessment, and leaving the drain in place for two weeks; antibiotics, analgesics, and anti-edema drugs; dye complications; assessment of breast recurrence; assessment of axillary recurrence; assessment of another breast; and four-month follow-up are all recommended.

2.4. Statistical analysis

IBM SPSS Version 20.0 was used for the statistical analyses. The data was displayed and properly analysed in accordance with the nature of the data collected for each parametric.

Mean, Standard deviation, and range (for adjustable numerical data) and Frequency and proportion

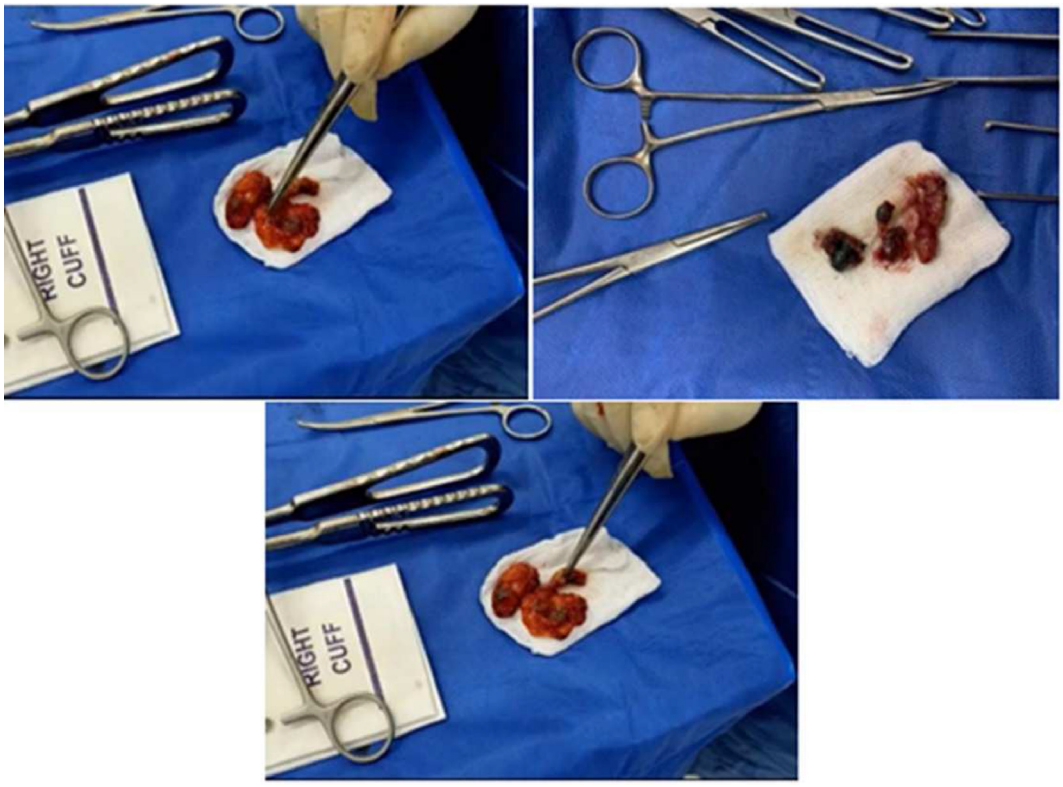

Fig. 4. Stained SLNs removed for frozen section.

Fig. 5. Marking and skin elliptical incision for lumpectomy.

(for non-numerical data) are examples of descriptive statistics. A Chi-square test was used to analyse the correlation between two qualitative factors.

3. Results

Demographic characteristics of the studied patients are summarized in (Table 1).

Tumor characteristics, staging, biopsy, identification of nodes, FzS of SLN compared to FzS, procedures for breast mass, final pathology result of the mass and subtypes of breast cancer are shown in (Table 2).

Complications which appeared were seroma in one case, infection in one case, and lymphedema in one case.

There was no statistically significant difference in pathological results of stained and non-stained LNs and pathological results of SLN according to a level where it diagnosed (Table 3).

Notable differences were found between among positive, negative and suspicious. FzS (was done for SLNB in 17 cases where SLN was diagnosed) revealed 4 cases were positive, 12 cases were negative, and one case was suspicious. As regarded the final pathology of specimens, one case was false negative (5.9%), and one case was false positive (5.9%) (Table 4).

Notable differences were found between ALND and SLNB (P value = 0.007). Notable differences were found between ALND and SLNB (P value = 0.006). The total number of LNs that were removed from 20 patients was 164 nodes. 105 nodes were removed by ALND (16 nodes were positive and 89 nodes were negative by histopathological examination), and 59 nodes were removed as SLNB (one of them was positive and 58 nodes were negative by histopathological examination) (Table 5).

Notable differences were found between stained and non-stained LNs (P value = 0.019). Pathological results showed that present 1 positive stained LN (1.7%) and 58 negative stained LNs (98.3%). 6 positive non-Stained LNs (14.2%) and 36 negative Non-Stained LNs (85.8%) (Table 6).

Table 1. Demographic data of the studied patients.

Age (years) **Mean ± SD**	50.2 ± 7.8
Age groups	
35–45	4 (20%)
45–55	10 (50%)
>55	6 (30%)
Family history	
Positive	18 (90%)
Negative	2 (10%)
Breast size (cup)	
A	2 (10%)
B	3 (15%)
C	6 (30%)
D	7 (35%)
E	2 (10%)

4. Discussion

One of the largest trials on SLNB to date is the B-27 research conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), following NACT. With an 84.8% recognition rate, 428 individuals received SLNB with ALND simultaneously following NACT using the blue dye isosulfan blue.[5] Compared with other studies, this research showed that 1% MB has an identification rate of 83%. Other studies showed comparable rates while using different detection agents, such as isosulfan blue dye. Yet, they were all considered to be insufficient if used alone, and studies showed better results when a dual agent tracer was used in the detection of SLNs.[6]

Table 2. Tumor characteristics, staging, biopsy, identification of nodes, frozen section of SLN compared to frozen section, procedures for breast mass, final pathology result of the mass and subtypes of breast cancer.

Tumor characteristics	$N = 20$
Lump discovery	
Accidently	10 (50%)
Self-examination	3 (15%)
Screening prog	7 (35%)
Method of tumor detection	
Physical	11 (55%)
Mammogram	7 (35%)
U/S	2 (10%)
Breast side	
Right	12 (60%)
Left	8 (40%)
Tumor site according to quadrant	
UOQ	9 (45%)
LOQ	4 (20%)
Retro areolar	4 (20%)
LIQ	2 (10%)
UIQ	1 (5%)
Tumor staging	
Breast advanced	6 (30%)
Axillary advanced	3 (15%)
Inflammatory breast cancer	2 (10%)
Mixed	9 (45%)
Tumor biopsy	
IDC	15 (75%)
ILC	3 (15%)
Mixed	2 (10%)
Identification of nodes	
Stained LNs	17 (85%)
Non stained LNs	3 (15%)
Frozen section of SLN compared to frozen section.	$N = 17$
Negative	12 (70.59%)
Positive	4 (23.53%)
Suspicious	1 (5.88%)
Procedure for breast mass	
BCS	11 (55%)
Lateral mammoplasty	2 (10%)
Skin sparing with LD flap	2 (10%)
MRM	3 (15%)
Reduction mammoplasty	1 (5%)
Simple mastectomy	1 (5%)
Final pathology result of the mass	
IDC	13 (65%)
IDC with in situ component	2 (10%)
ILC	3 (15%)
Mixed	2 (10%)
Subtypes of breast cancer	
A	10 (50%)
B	5 (25%)
Triple negative	2 (10%)
HER2 over expression	3 (15%)

BCS, Breast-conserving surgery; HER2, human epidermal growth factor receptor 2; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma; LD, latissimus dorsi; LIQ, Lower inner quadrant; LNs, lymph nodes; LOQ, lower outer quadrant; MRM, Modified radical mastoidectomy; U/S, Ultrasound; UIQ, Upper inner quadrant; UOQ, Upper outer quadrant.

Table 3. Pathological results of stained and non-stained LNs and pathological results of SLN according to level where it diagnosed.

	Positive *N* (%)	Negative *N* (%)	Total *N* (%)	*P* value
Stained	4 (23.53%)	13 (76.47%)	17 (85%)	0.202
Non-Stained	2 (11.76%)	1 (5.88%)	3 (15%)	
Level I	2 (11.76%)	11 (64.71%)	13 (76.47%)	0.059
Level II	2 (11.76%)	1 (5.88%)	3 (17.6%)	
Level III	0 (0)	1 (5.88%)	1 (5.88%)	

Table 4. Final pathology of SLN compared to frozen section.

Frozen section for SLN	Final histopathological examination			*P* value
	Positive *N* (%)	Negative *N* (%)	Total *N* (%)	
Positive	3 (17.6%)	1 (5.9%)	4 (23.5%)	**0.021***
Negative	1 (5.9%)	11 (64.7%)	12 (70.6%)	
Suspicious	0 (0%)	1 (5.9%)	1 (5.9%)	
Total	4 (23.5%)	13 (76.5%)	17 (100%)	

SLN, Sentinel lymph node.

Table 5. Pathology of LN in ALND and SLNB and number of total LNs (sentinel and nonsentinel) removed and their pathology.

Pathology of LN in ALND and SLNB.				
	Positive *N* (%)	Negative *N* (%)	Total *N* (%)	*P* value
ALND	5 (71.4%)	2 (28.6%)	7 (100%)	**0.007**[as]
SLNB	1 (7.7%)	12 (92.3%)	13 (100%)	
Number of total LNs (sentinel and nonsentinel) removed and their pathology.				
ALND	16 (15.23%)	89 (84.76%)	105 (100%)	
SLNB	1 (1.7%)	58 (98.3%)	59 (100%)	

ALND, Axillary lymph node dissection; SLNB, Sentinel lymph node biopsy.

[a] Significant (*P* value < 0.05).

Table 6. Number of SLNs and nonstained cases and their pathology.

	Positive *N* (%)	Negative *N* (%)	Total *N* (%)	*P* value
Stained	1 (1.7%)	58 (98.3%)	59 (100%)	**0.019***
Non-Stained	6 (14.2%)	36 (85.8%)	42 (100%)	

In the present research, FzS (was done for SLNB in 17 cases where SLN was diagnosed) revealed 4 cases were positive, 12 cases were negative, and one case was suspicious. SLNs were diagnosed only in 5 cases of the first 7 cases, in 6 cases of the second 7 cases and in 6 cases of the last 6 cases. Role of FzS in SLNB for breast cancer was studied by Lombardi et al.[7] and they documented that a total of 1226 (86%) patients underwent FZS; of these patients, 146 (11.9%) were false negatives. The global sensitivity of FZS in detecting both macro and micrometastases was 53.7%.

Experience seems to shorten the time it took to spot SLNs according to results of this research. The median duration of the 17 cases in which SLN was identified ranged from 20 min in the first 6 cases to

16 min in the second 6 cases and 14 min in the third 5 cases. Also, Ramadan et al.[8] assessed how well the axillary SLNB with methylene blue injection approach works for patients with breast cancer that has spread to the chest wall. They found that it took an average of 45 min from when the methylene blue was injected till when the SLN(s) were identified and dissected.

In the current research, BCS occurred in 11 cases (55%), Lateral mammoplasty occurred in 2 cases (10%), Skin sparing with LD flap occurred in 2 cases (10%), MRM occurred in 3 cases (15%), Reduction mammoplasty occurred in one case (5%) and Simple mastectomy occurred in one case (5%). Our results are in harmony with Sanchez et al.[9] who reported that conservative surgery occurred in 142 (64.8%), conservative mastectomy occurred in 68 (31.1%) and simple mastectomy in 9 (4.1%).

In the present research, subtype A of breast cancer was present in 10 cases (50%), subtype B of breast cancer was present in 5 cases (25%), subtype triple negative of breast cancer was present in 2 cases (10%) and subtype HER2 over expression of breast cancer was present in 3 cases (15%). In Sanchez et al.[9] research, luminal A represented 46 (21%), luminal B 70 in (32%), HER2 in 4 (1.8%) and triple negative in 22 (10%).

According to our results, complications which appeared were seroma in one case, infection in one case and lymphedema in one case. Similar to our findings, Yap et al.[10] assessed SLNB out 75 outcomes using blue dye method and reported that of 95 SLNB-only cases, The establishment of a seroma was observed in 46 cases (61.3%). After a negative SLNB, one patient experienced arm paresthesia, and two others experienced recurrences in the local (chest wall) and axillary regions. There was no instance of lymphedema among the patients.

Our results revealed that pathological results showed that positive stained LNs were present in 4 cases (23.53%) and negative stained LNs were present in 13 cases (76.47%). Positive Non-Stained LNs were present in 2 cases (11.76%) and the negative Non-Stained LNs were present in 1 case (5.88%). Similar to our findings, Khallaf et al.[6] documented that regarding SLN identification, SLN was successfully identified using 1% MB in 26 patients, with an identification rate of 83% (26/31). Back-up ALND was then done, and the results of LN status in ALND were compared with those of the SLN. One out of the five cases in which SLN was not identified had positive ALN deposits. SLN was positive in 20 of 26 cases; of the six cases that showed negative SLNs, three cases were concomitant with the ALND results, whereas the other three cases were falsely negative, with positive tumor deposits in ALND specimens. Thus, the FNR was 3/26 (11.5%) in the whole group.

In the current research, levels of axillary LN (where SLN was diagnosed in 17 cases) was 13 cases (76.47%) at level I, 3 cases (17.6%) at level II and one case (5.88%) had SLN at level III.

Khallaf et al.[6] reported that regarding response in the axilla, seven patients showed complete pathological response in the axilla, with a percentage of 22.5%. However, the overall tumor complete pathological response was found in six patients, with a percentage of 19.4%.

In this research, Notable differences were found between among positive, negative and suspicious. FzS (was done for SLNB in 17 cases where SLN was diagnosed) revealed 4 cases were positive, 12 cases were negative, and one case was suspicious. As regarded final pathology of specimens, one case was false negative (5.9%), and one case was false positive (5.9%).

In the current research, Notable differences were found between ALND and SLNB (P value = 0.007). ALND revealed 5 cases (25%) were positive and 2 cases (10%) were negative. SLNB revealed one case (5%) was positive and 12 cases (60%) were negative.

In Sanchez et al.[9] research, The overall SLN detection rate was 96.8% (98.2% in cN0-ycN0 patients and 95.2% in cN + -ycN0 patients). Most people had three LNs surgically removed. There were 149 confirmed ypN0(sn) cases among cN0-ycN0 patients (68%), and 86 confirmed ypN0(sn) cases among cN1/2-ycN0 patients (47.8%).

However, Yamamoto et al.[11] reported that When forecasting the status of the axilla, the SLN was 95% accurate (19/20). False-negative results on SLNs were found in 4 of 7 patients, with a false-negative incidence of 14% (1/7). Overall, the SLNB had a sensitivity of 85.7% (6/7) and a negative prognostic value of 93.0% (13/14).

In the present research, Notable differences were found between ALND and SLNB (P value = 0.006). The total number of LNs that were removed from 20 patients was 164 nodes. 105 nodes were removed by ALND (16 nodes were positive and 89 nodes were negative by histopathological examination), and 59 nodes were removed as SLNB (one of them was positive and 58 nodes were negative by histopathological examination). The extreme number was given by Giuliano et al.,[12] that was 8 SLNs. In our idea 8 LNs is a large figure similar to sampling and it goes the concept of sentinel lymphadenectomy. This appears infrequently and may be the result of a time lag between dye injection and node detection. The presence of anthracosis of airway origin in the

axillary nodes is a potential stumbling block because it can give the involved lymph node a bluish-gray colour and lead to erroneous identification of an SLN.

Limitations include It was a single-center research, and the results may differ elsewhere and a relatively small sample size may affect our conclusions. We recommend Further clinical studies with larger sample size and multicenter cooperation to validate our findings and future studies comparing the efficacy of SLNB with patent blue stain with other types of stains are also required. Dual technique (radiocolloid and blue dye) for SLNB identification is still highly recommended for more accuracy. For comparison, involvement of tumors in other locations of the breast and the use radiocolloid are required.

4.1. Conclusion

SLN detection rate was 85%, ALND revealed 5 cases (25%) were positive and 2 cases (10%) *were negativ*e. SLNB revealed one case (5%) was positive and 12 cases (60%) were negative. SLN detection rate definitely rose with experience, suggesting the existence of a learning curve.

Authors' contribution

Ahmed Mohamed Sheta: Idea formulation, data collection, analysis and writing. Mohamed Mamdouh Asar: data collection and writing. Ashraf Abd-Elhamid Abd-Elmonem: Supervision, writing, and revision.

Source(s) of support

Nil.

Conflicts of interest

Nil.

Acknowledgements

Nil.

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