Concurrent radiation therapy and docetaxel in adjuvant treatment of locally advanced breast cancer

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Introduction
Locally advanced breast cancer (LABC) and inflammatory breast cancer refer to a diverse and heterogeneous group of breast cancers. Patients with these cancers include those with operable disease at presentation (AJCC clinical stage T3 N1M0), inoperable disease at presentation (AJCC clinical stage T4 or N2 to 3M0), and inflammatory breast cancer (AJCC clinical stage T4dN0 to N3M0) [1]. This group represents only 2% to 5% of all breast cancers in the United States (1) while in Egypt, patients usually present with advanced stage of cancer [2].

Purpose: To assess the safety and efficacy of the use of concurrent radiation therapy and docetaxel in adjuvant treatment of locally advanced breast cancer (LABC).

Patients and methods: Between February 2009 and January 2013, 62 patients with LABC who underwent primary mastectomy or neoadjuvant chemotherapy (FEC) followed by mastectomy at Assiut University Hospitals were entered into this trial. Three to five weeks after mastectomy or after the last dose of adjuvant FEC, patients were given concurrent chemoradiotherapy. Weekly intravenously docetaxel (30 mg/m²) was given over 9 weeks.

Results: The median follow-up for all patients is 32 months (range 12–63). Forty-eight patients (77.4%) remain alive, 12 patients (19.4%) died due to breast cancer, and 2 (3.2%) from other nonrelated causes. The 3-year rate of local recurrence free survival (LRFS) and disease free survival (DFS) were 93.8% (95% CI, 87.8–99.8%) and 70.2% (95% CI, 58.8–81.6%, Figure 1) respectively. The 3-year overall survival rate was 89.4% (95% confidence interval [95% CI], 81.7–97.1%; Figure 2). Four (6.4%) patients experienced locoregional recurrence as the first site of recurrence and 22 (35.5%) patients developed distant metastases. Acute toxicities were moderate during concomitant chemoradiotherapy. Five patients (8.1%) had grade 3–4 radiation dermatitis. Grade 3–4 radiation pneumonitis developed in 2 patients. Long-term toxicity was rare.

Conclusion: Concurrent docetaxel and radiotherapy is an acceptable adjuvant regimen for patients with LABC. Although it does not apparently improve local control and/or survival, it shortened total treatment time, and was well tolerated.

Keywords: Concurrent radiation therapy, docetaxel, breast cancer

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considered for carefully selected patients. Adjuvant radiation to the breast, chest wall, and draining lymphatics should be offered to all patients with clinical stage III disease [4].

The optimal way to integrate chemotherapy and radiation therapy (RT) after breast surgery for patients with breast cancer remains unknown [5]. However, the current standard is chemotherapy followed by whole-breast-irradiation (WBI). The delay of RT induced more frequent local recurrences [6-8]. From pooled data of 10 retrospective studies, delaying RT in favour of chemotherapy increased the risk of local relapse to 16% from 6% [9]. Concurrent treatment allows RT and chemotherapy to start temporally, shortens the duration of therapy, and potentially improves local control via the radiation sensitizing effects of chemotherapy [10].

Anthracyclines and taxanes are the backbone of most modern breast chemotherapy regimens. Anthracycline-based concurrent chemoradiotherapy (CCRT) has been associated with serious skin and cardiac toxicity [11]. The concurrent use of taxanes and WBI seems feasible. Taxanes are mitotic inhibitors that stabilize microtubules by promoting their assembly and preventing depolymerization [12,13]. After exposure to the taxanes, cells are arrested in the G2/M phase of the cell cycle, which is known to be the most radiosensitive phase of the cell cycle [14,15]. Docetaxel has been studied in combination with radiation in other solid tumors with favorable results. In phase II trials, the most commonly used schedule with concomitant radiation was docetaxel at 20 to 30 mg/m² per week [16].

The present study addressed the use of concurrent radiation therapy and docetaxel in adjuvant treatment of locally advanced breast cancer.

**Patients and methods**

Between February 2009 and Jan. 2013, 62 patients with locally advanced breast cancer who underwent primary modified radical mastectomy (MRM) or neo adjuvant chemotherapy followed by MRMat Assiut University Hospitals were entered into this pilot prospective trial. Patients should fulfill the following criteria.

**Inclusion criteria**

- **Histological diagnosis of invasive adenocarcinoma of the breast.**
- **AJCC clinical stage III at presentation.**
- **Age ≥18 and ≤70 years old.**
- **Performance status (Karnofsky index) ≥ 80.**
- **Complete stage workup during the 4 weeks prior to the start of treatment.** All patients must have baseline measurements of breast and nodal lesions. All patients must have a bilateral mammogram, computed tomography (CT)-scan of the chest and abdomen and echocardiography. If there was bone pain, and/or alkaline phosphatase elevation, a bone scan tigraphy was mandatory.
- **Laboratory results (within 14 days prior to the start of adjuvant treatment):** Hematology: neutrophils ≥1.5x10⁹/l; platelets ≥100x10⁹/l; hemoglobin ≥10 mg/dl; Hepatic function: total bilirubin ≤1 upper normal limit (UNL); SGOT and SGPT ≤2.5 UNL; alkaline phosphatase ≤2.5 UNL. Renal function: creatinine ≤175 umol/l (2 mg/dl).

**Exclusion criteria**

- **Prior radiotherapy for breast cancer.**
- **Bilateral invasive breast cancer.**
- **Pregnant or lactating women.**
- **Any M1 tumor.**
- **Pre-existing grade ≥2 motor or sensorial neurotoxicity (National Cancer Institute Common Toxicity Criteria version 2.0 [NCI CTC v-2.0]).**
- **Any other serious medical pathology, such as congestive heart failure; unstable angina; history of myocardial infarction during the previous year or high risk arrhythmias.**

**Treatment plan**

Patients who didn't receive neoadjuvant chemotherapy were given the same regimen in the adjuvant sitting. Neoadjuvant or adjuvant chemotherapy used in this study represented a standard anthracycline-based regimen. It consisted of three cycles of intravenous 5-fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (500 mg/m²) administered every three weeks (FEC) [17].

Three to five weeks after mastectomy or after the last dose of adjuvant FEC, patients were given concurrent chemoradiotherapy. Weekly intravenously (IV) docetaxel (30 mg/m²) was given over 9 weeks, with daily external beam radiation therapy (RT) administered concurrently during the first five to six weeks. RT started the day of the first docetaxel cycle and was given at least 2 hours after finishing docetaxel infusion. All patients were premedicated with IV dexamethasone 8 mg, ondansetron 8 mg IV, and ranitidine 50 mg IV infusion 30 minutes before chemotherapy.

**Radiation therapy technique**

The target volumes included treatment to the chest wall and draining lymphatic when indicated. The supraclavicular nodal region was treated in patients who had 4 or more involved axillary nodes or any number of involved axillary nodes with extracapsular extension. Additional axillary radiation was given when axillary dissection was inadequate, defined as Level I and II nodes not resected or fewer than 10 nodes removed, and was also given when there was gross residual disease in the axilla. The axilla was not specifically targeted for cases of extracapsular extension after lymph node dissection. Internal mammary nodes were not specifically targeted. Patients were immobilized with their ipsilateral arm abducted (90 to 120 degrees) and externally rotated. Patients were placed on a 10- to 15-degree angle board to flatten the slope of the chest wall in the region of the sternum. The border between the chest wall and the supraclavicular fields is typically placed at the bottom of the clavicular head. Treatment portals consisted of opposing tangential fields using 6- to 10-MV photons. The lateral border of this field was matched to the photon tangent fields that were...
created with matched nondivergent deep and cranial borders. A nondivergent cranial border was created through rotation of the couch, and a nondivergent deep border was achieved by overrotating the gantry or a half-beam block. The collimators were rotated to match the chest wall slope, and any volume that extended into the supraclavicular field is blocked. These fields were matched to a supraclavicular/axillary apex field. All patients were planned with two-dimensional planning. All chest wall radiation fields were designed to avoid irradiating the heart. Initial fields and target volumes were treated to a total dose of 50 Gy in 25 fractions over 5 weeks. For patients with skin involvement a 5–10-mm bolus was applied for 50% of the dose every other day to cover skin and dermal lymphatics.

During chemoradiotherapy, patients were evaluated weekly for acute toxicity and compliance with the protocol. Clinical examination and complete blood count were performed. An absolute granulocyte count of less than 1,500/mm³ or a platelet count of less than 100,000/mm³ before each cycle resulted in a treatment delay of at least 1 week. Treatment was stopped if hematologic recovery took more than 5 weeks. No dose reductions were planned. RT was interrupted if grade 3 cutaneous or pulmonary toxicity occurred.

Concerning HER2 status, none of the patients with HER2 positive disease were treated with neoadjuvant or adjuvant trastuzumab, due to financial reasons. All women who showed to have estrogen receptor–positive and/or progesterone receptor–positive tumors were prescribed 20 mg daily of tamoxifen, which was started 3 weeks after the last dose of docetaxel.

The trial was approved by the ethics committee of the Faculty of Medicine, Assiut University, and all patients provided a written informed consent.

### Follow-up and end points
Patients were followed every three months for the first two years after the last cycle of adjuvant chemotherapy and thereafter every six months for 5 years. Mammography was performed annually. The primary end point was Disease free survival (DFS), defined as the time from enrolling in the study to the first treatment failure or death. Secondary end points were the incidence of adverse effects, local recurrence-free survival (LRFS) defined as the time from enrolling in the study to the first treatment locoregional relapse or death and overall survival (OS) calculated from the time of diagnosis to the time of the last follow-up visit or death.

### Toxicity evaluation
Skin, lung and esophageal toxicities were assessed according to the Radiation Therapy Oncology Group (RTOG) scale for acute and late effects. Other toxic side effects were scored according to National Cancer Institute Common Toxicity Criteria version 2.0 [NCI CTC v-2.0].

### Statistical analysis
The Kaplan-Meier method was used to estimate the rates of DFS, LRFS, and OS. Statistical analysis was performed using SPSS for Windows version 20.0 (SPSS, Inc., Chicago, IL).

### Results
Patients and disease characteristics are summarized in Table 1. Sixty-two patients were recruited in this study, 46 (74.2%) of them underwent neoadjuvant FEC followed by MRM. All of the remaining 16 patients who underwent primary MRM received 3 cycles of adjuvant FEC. Patients in clinical stages IIIA, -B, and -C were 38.7%, 45.2%, and 16.1% respectively. None of patients had inflammatory breast cancer. Underwent primary mastectomy or neoadjuvant chemotherapy followed by mastectomy. Estrogen receptor (ER)-positive expression was found in 56.5%, and in 54.8% for progesterone receptor (PgR). Low/moderate histological grade was 56.5, while high grade stood at 43.5%. Human epithelial growth factor receptor 2 (HER2) expression was found in 27.4%.

### Treatment compliance
Thirty eight (61.3%) patients received supraclavicular irradiation, and a posterior axillary supplement was used in eleven (17.7%) patients. RT treatment had to be interrupted in 13 (21%) patients; 5 (8.1%) of them were due to skin toxicity grade 3, six were due to machine malfunctions and two due to patient choice. Two patients received less than 50 Gy.

### Table 1. Patient and Tumor Characteristics.

<table>
<thead>
<tr>
<th>Patient and Tumor Characteristics</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menopausal status:</strong></td>
<td></td>
</tr>
<tr>
<td>Pre/perimenopausal</td>
<td>32 (51.6)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>30 (48.4)</td>
</tr>
<tr>
<td><strong>T- stage</strong></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>38 (61.3)</td>
</tr>
<tr>
<td>T4</td>
<td>24 (38.7)</td>
</tr>
<tr>
<td><strong>N- stage</strong></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>5 (8.1)</td>
</tr>
<tr>
<td>N1</td>
<td>19 (30.6)</td>
</tr>
<tr>
<td>N2</td>
<td>23 (37.1)</td>
</tr>
<tr>
<td>N3</td>
<td>15 (24.2)</td>
</tr>
<tr>
<td><strong>TNM stage</strong></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>15 (24.2)</td>
</tr>
<tr>
<td>IIA</td>
<td>17 (27.4)</td>
</tr>
<tr>
<td>IIB</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>IIC</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (8.1)</td>
</tr>
<tr>
<td>II</td>
<td>30 (48.4)</td>
</tr>
<tr>
<td>III</td>
<td>27 (43.5)</td>
</tr>
<tr>
<td><strong>Estrogen receptor</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>27 (43.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>35 (56.5)</td>
</tr>
<tr>
<td><strong>Progesterone receptor</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>28 (45.2)</td>
</tr>
<tr>
<td>Positive</td>
<td>34 (54.8)</td>
</tr>
<tr>
<td><strong>HER2/neu</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>39 (62.9)</td>
</tr>
<tr>
<td>Positive</td>
<td>23 (37.1)</td>
</tr>
</tbody>
</table>
Three patients (4.8%) of the whole group developed grade 1-2 hypersensitivity reactions to docetaxel (in the form of palpitation and chest pressure) and they were re-challenged successfully with slower rates of infusion. Three patients discontinued docetaxel after the third to sixth weekly doses due to grade III neuropathy.

**Outcome and pattern of failure (Table 2)**

The median follow-up for all patients is 32 months (range 12–63). Forty-eight patients (77.4%) remain alive, 12 patients (19.4%) died due to breast cancer, and 2 (3.2%) from other nonrelated causes. The 3-year rate of LRFS and DFS was 93.8% (95% CI, 87.8–99.8%) and 70.2% (95% CI, 58.8–81.6%, Figure 1). The 3-year overall survival rate was 89.4% (95% confidence interval [95% CI], 81.7–97.1%; Figure 2). Four (6.4%) patients experienced locoregional recurrence as the first site of recurrence and 22 (35.5%) patients developed distant metastases. First sites of distant metastases were as follows: bone (16.1%), lung (6.4%), liver (4.8%) and brain (3.2%). Four patients had more than one recurrence site.

**Toxicity**

Both acute locoregional and Acute systemic toxicities were moderate during concomitant chemoradiotherapy. Table 2 shows the incidences of grade 3/4 toxicities during concomitant chemoradiotherapy. Five patients (8.1%) had grade 3-4 radiation dermatitis. Grade 3-4 radiation pneumonitis developed in 2 patients.

Regarding docetaxel-induced systemic toxicity, seven patients (11.3%) developed grade 3-4 neutropenia, six (9.7%) had grade 3-4 anaemia and three (4.8%) had grade 3-4 thrombocytopenia. Grade 3-4 neuropathy occurred in three patients. There was no grade 3-4 gastrointestinal toxicity.

Long-term toxicity was rare. Skin pigmentation and telangiectasia were recorded in 8.1%, and 3.2% of the study patients respectively. Each of radiation pneumonitis, and esophagitis were recorded in 3.2% of the study patients. There were no cases of subcutaneous fibrosis, brachial plexopathy or rib fracture.

**Discussion**

This trial was conducted to evaluate the impact of adjuvant concurrent RT and CT in locally advanced breast cancer. The main advantages of CCRT are: 1. delivering both treatments of CT and RT at same time; 2. Biologicalsynergy effect that can increase the efficacy of the treatment [18]. Early experiences with concurrent chemoradiation in early-stage breast cancer were evaluated in CMF-based chemotherapeutic regimens [19-22]. Although that treatment had an acceptable toxicity profile and a shortened overall treatment time, clinical benefit in terms of OS or DFS has not consistently been shown [11]. Moreover, CMF regimens are no longer commonly used. Since that initial experience, the feasibility of concurrent
therapy has been explored in other chemotherapy regimens. Few prospective studies investigated CCRT using anthracycline regimen [23-26]. Fiets et al., [24] showed high rate of high grade skin toxicity, and more cardiac dysfunction, and concluded that this protocol cannot be used in practice. On the other hand, a retrospective study by Smaili et al., compared 2 adjuvant treatments using CCRT, the first with anthracycline (group A) and the second with CMF (group B). At 5 years, the isolated LRFS was significantly higher in group A compared to group B (98.7% vs 95.3%; P=0.034). In addition, the use of anthracycline regimens was associated with a higher rate of 5 years EFS (80.4% vs 75.1; P=0.057). The 5 years OS was 83.2% and 79.2% in the anthracycline and CMF groups, respectively (P=0.143) [10]. However, these results may be explained by the effect of anthracycline regimen and not by the use of CCRT [26].

In a multicentre randomized trial (Arcoseintrial), CNF (mitoxantrone 12 mg/m², in combination with cyclophosphamide 500 mg/m² and fluorouracil 500 mg/m²) every 21 days for 6 cycles, with RT starting during cycle 1, was compared with sequential CNF and RT. Unfortunately, the concurrent regimen failed to show any benefit in 5-year DFS and OS [27,28]. The 5-year DFS was 80% in both groups; P=0.83, LRFS was 92% in sequential versus 95% inconcurrent; P=0.76, and OS was 90% in sequential versus 91% in concurrent; P=0.76. Nevertheless, concurrent treatment was shown to improve local control in lymph-node-positive patients (the 5-year LRFS was 97% in concurrent v 91% in sequential; P=0.02).

Similar results were seen in a French multicentre trial comparing concomitant CNF and RT with CEF (cyclophosphamide–epirubicin–5-fluorouracil) and sequential RT [29]. Unfortunately, mitoxantrone has been associated with high rates of leukemic transformation; it is therefore now rarely used [11].

Taxanes may be a better choice for concurrent therapy than CMF and anthracyclines because of the former’s radiation sensitizing properties [30,31]. The advantages of concurrent chemoradiation with taxanes have been well documented in the treatment of other malignancies such as lung [32,33]. However, the published literature regarding the concurrent administration of taxanes and RT in the treatment of breast cancer consists of small trials using varying treatment schedules and doses [34-40] providing no consensus. Paclitaxel was evaluated for concurrent therapy both in the neoadjuvant and adjuvant settings.

In the neoadjuvant setting, two phase i/ii prospective trials, one by Skinner et al., [41] and the second by Kao et al., [42], in 29 and 33 patients with breast cancer respectively, showed a benefit from concurrent paclitaxel and RT, especially in locoregional control. Skinner et al., concluded that CCRT provides significant pathological response, in up to 33% of patients with locally advanced breast cancer, but with a significant postoperative morbidity rate. With a median follow-up of 43.8 months, Kao et al., reported 4-year actuarial locoregional control, disease-free survival, and overall survival of 83%, 33%, and 56% respectively.

In the adjuvant setting, Chen et al., [43] evaluated Concurrent paclitaxel chemotherapy and radiotherapy in 44 women with node-positive Stage II and III breast cancer. Radiotherapy was concurrent with the first 2 cycles of adjuvant paclitaxel. The 5-year DFS was 88%, and OS was 93%. There were no local failures [43].

Although docetaxel is highly active against breast cancer and more potent than paclitaxel in promoting tubulin polymerization, it is less well studied as concurrent therapy with radiation in breast cancer. In the neoadjuvant setting, only a few studies have been published on radiation with concurrent docetaxel in breast cancer [36,44]. Karasawa et al., investigated whether the addition of docetaxel (40 mg/m² biweekly) to radiotherapy enhanced tumor response in patients with advanced or recurrent breast cancer. The rates of CR, PR, SD, and PD for all patients were 40%, 37%, 11% and 11%, respectively. CR and PR rates were 9% and 82% for advanced disease patients, 54% and 17% for recurrent patients. Overall survival rates at 1 and 2 years after treatment were 83% and 49%, respectively [44]. Two other phase i/ii Canadian studies of neoadjuvant concurrent radiation with weekly docetaxel (30-35 mg/m²) in patients with locally advanced non-inflammatary breast cancer (otc 1159 and otc 1202) are under way, but have yet to report results [11].

In the current study, the 3-year OS and DFS rates were 89.4% and 70.2% respectively. These results are comparable to rates observed in a retrospective analysis done in our University [2]. This analysis assessed different sequential protocols and not concomitant chemotherapy and radiotherapy in LABC. DFS was estimated at 2.5 years, and it was 83.5%, 82.3% and 80% for patient receiving radiation before chemotherapy [group A], sandwich [group B] and after finishing chemotherapy [group C] respectively (P>0.5). In another similar Egyptian retrospective analysis, Abu-Hamar et al., reported 5-year OS and DFS and LRFS rates of 71.8%, 67.6% and 90.9% respectively [45]. A similar 3-year LRFS (93.8%) was found in our patients indicating that no benefit was added from docetaxel as a radiosensitizer.

In our study we did not observe excessive toxicity with concurrent radiation treatment and docetaxel. Five patients (8.1%) had grade 3-4 radiation dermatitis while grade 3-4 radiation pneumonitis developed in 2 patients. Other investigators found some what different results, most likely because of differences in the details of both the chemotherapy agents and doses and radiotherapy. No cases of pneumonitis were reported to have occurred in a group of 202 patients treated at the Princess Margaret Hospital in Toronto with concurrent radiotherapy and CMF [22]. Five percent of patients (4 of 87 patients) in a report of the “triple M” program of the Royal Marsden Hospital [47] developed symptomatic radiation pneumonitis within 6 weeks of completing radiotherapy. The investigators found that the risk of pneumonitis was correlated with having 3 cm of lung in the tangential radiation field.

A prospective study from William Beaumont Hospital tested RT and concurrent paclitaxel (175 mg/m²) delivered every 21
days. The authors noted that radiation pneumonitis developed in 4 patients (20%), and 13 (65%) had Grade 2 cutaneous toxicity or higher [34]. In a retrospective analysis of the Massachusetts General Hospital experience, Taghian et al., [35] reported a 15% risk of pneumonitis in 21 patients treated with concurrent paclitaxel and radiation as compared with an institutional incidence of 1% among women not treated with paclitaxel. Recently, Chen et al., [43] reported that none of 44 patients had pneumonitis requiring steroids and acute Grade 3 skin toxicity was developed in only 2 patients.

On the other hand, a retrospective analysis from the University of Washington evaluated 44 women who received RT concurrent with either paclitaxel or docetaxel chemotherapy. There were no reports of pneumonitis although a 20% rate of Grade 3 acute skin toxicity was seen. However, this group was more heterogeneous in treatment schema [36]. Hanna et al., [34] reported a higher-than-expected rate of radiation-induced pulmonary toxicity. They noted an increased rate of toxicity among those treated with MRM, which may be related to RT dose/field size. In the study conducted by Tapen et al., [45], all patients had radiation dermatitis. Four patients (8%) had grade 3 desquamation; none had grade 4 or 5. Chest wall/axillary or arm pain occurred in eleven patients. Grade 1-2 or grade 3 hematologic toxicity occurred in six and two patients respectively. Grade 1 neuropathy in three patients. Grade 1-2 nausea/vomiting occurred in eight patients. Grade 1-2 diarrhea occurred in three patients [45].

In accordance to the previous studies [22, 34-36,43-46], late toxicity was unusual in the current trial. Skin pigmentation and telangectasia were recorded in 8.1%, and 3.2% of the study patients respectively. Each of radiation pneumonitis, and esophagitis were recorded in 3.2% of the study patients. There were no cases of subcutaneous fibrosis, brachial plexopathy or rib fracture.

We acknowledge some of the limitations of the current study. First, the sample size was too small to meaningfully stratify the patients’ outcome by the risk factors. Second, the follow up period was relatively short and longer period is needed to confirm our results.

**Conclusion**

Our study showed that concurrent docetaxel and radiotherapy is an acceptable adjuvant regimen for patients with LABC. Although it does not apparently improve local control and/or survival, it shortened total treatment time, and was well tolerated without significant pulmonary toxicity. Longer follow up and larger randomized controlled clinical trials are needed to determine whether this regimen is superior to sequential regimens and to confirm the validity of such a strategy.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

All authors shared in research design and conduction and analysis of data. The main author (AlGizawy SM) wrote the paper and had primary responsibility for final content. All authors read and approved the final manuscript.

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