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RESEARCH ARTICLE

A Study of Lactate Dehydrogenase (LDH) Levels and Other Biomarkers in Breast Cancer Patients Undergoing Chemotherapy: Implications for Prognosis and Monitoring

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Abstract

Background: Breast cancer, after lung cancer, is the second leading cause of cancer-related deaths worldwide, making early diagnosis and continuous treatment crucial. This study evaluated the levels of serum lactate dehydrogenase (LDH) enzyme and other biochemical parameters in post-operative chemotherapy in Iraqi women diagnosed with breast cancer. This study highlights the potential use of LDH as a biomarker for monitoring treatment response, rather than being limited to its traditional diagnostic role.

Objective: To assess the prognostic value of serum LDH along with other biochemical markers, such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrolytes (Na^+, K^+, and Cl^-), kidney functions (urea and creatinine), and prolactin hormone.

Methods: A cross-sectional study was conducted on 150 serum samples collected from 100 female patients diagnosed with breast cancer (after surgery and during chemotherapy) and 50 age-matched healthy women, aged 26–60 years, as a control group. The samples were collected at Al-Amal National Hospital for Cancer Management, Medical City, Baghdad, Iraq, from July 2021 to October 2021. All biochemical parameters (LDH, ALP, ALT, AST, Na^+, K^+, Cl^-, urea, creatinine, and prolactin) were measured in the hospital laboratory using standard automated biochemical analyzers and commercially available diagnostic kits.

Results: LDH activity was significantly elevated in breast cancer patients, highlighting its potential as an early prognostic marker for progression or recurrence of disease. Renal function tests (urea and creatinine) and liver enzymes (ALT and AST) were significantly higher in patients, compared to controls ($P < 0.05$). Electrolytes, specifically K^+ and Cl^-, were elevated ($P < 0.05$), while Na^+ showed no significant difference ($P > 0.05$). Levels of ALP were not significantly different between patients and controls ($P > 0.05$). Level of prolactin hormone was also significantly higher in patients ($P < 0.05$) than in controls. These findings underscore LDH as a central prognostic marker, with other biochemical parameters providing supportive information on patient status.

Conclusion: Elevated serum LDH levels in breast cancer patients may serve as an early prognostic marker for progression or recurrence of disease, offering a practical tool for monitoring response to treatment.

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Introduction

Cancer is characterized by uncontrolled cell growth leading to the formation of tumors, which may be benign—localized and slow-growing—or malignant, with the ability to invade and spread [1–4]. Breast cancer is among the most common malignant tumors worldwide, with over two million new cases reported annually [5,6]. Several risk factors, such as obesity, physical inactivity, and alcohol consumption, increase its incidence, while early detection remains critical for improving outcomes [7–9]. Patients may present with symptoms such as nipple changes, tissue heterogeneity, or unexplained weight loss [8,10]. Breast cancer can be invasive, spreading to surrounding tissues, or non-invasive, restricted to ducts or lobules, with treatment varying accordingly [11].

Breast cancer is characterized by a long doubling time of cancer cells (100–300 days), which provides a valuable opportunity for early detection and treatment. The classification of breast cancer is based on tumor size, lymph node involvement, and the presence of metastasis. Stage 0: the tumor is confined to the site of origin. Stage 1: the tumor spreads into fatty tissue of the breast. Stage 2: The tumor increases in size and may extend further within the breast. Stage 3: The tumor involves nearby lymph nodes and the chest wall. Stage 4 (metastatic stage): The tumor spreads to distant organs, such as bones, liver, lungs, and brain [13,14].

Early diagnosis, adjuvant chemotherapy, hormonal therapy, and radiotherapy play a major role in the treatment of breast cancer and in reducing disease-related risks [15]. Both estrogen (ER) and progesterone (PR) receptors are considered predictive factors in breast cancer. Radical mastectomy was applied in the early 20th century but proved less efficient compared to less severe surgical approaches. Chemotherapy, endocrine therapy, and anti-human epidermal growth factor receptor 2 (HER2)-targeted therapy have demonstrated high efficacy in reducing breast cancer risks and improving the survival [16]. Breast cancer is a heterogeneous disease, and in cases of small tumors, locoregional treatment may be sufficient, whereas cancer that has spread to distant sites requires additional therapy. The main goals of treatment are surgical resection, sampling, and removal of axillary lymph nodes, followed by radiation [17].

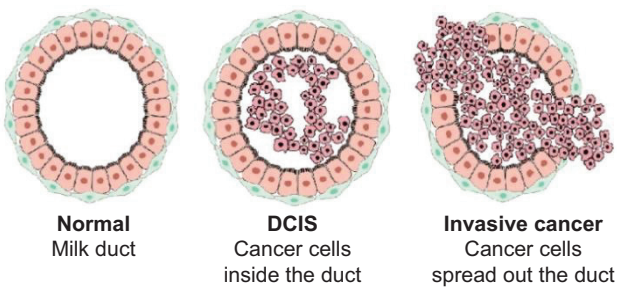

Figure (1): Difference between normal cells lining the milk duct, ductal carcinoma *in situ* (DCIS), and invasive cancer [12].

In order to better understand disease progression and treatment response, biomarker analysis has become an essential tool. Histological grade, obtained via core needle biopsy (CNB), axillary status, and tumor size are important parameters in breast cancer. Estrogen receptor alpha (ER-α) is a key predictive factor for advanced-stage patients responding to hormone therapy, which is nontoxic and suitable for long-term use [18]. Cancer antigen CA15.3 is elevated pre-surgically and serves as an important marker for evaluating response after chemotherapy [19].

Among emerging biomarkers, serum lactate dehydrogenase (LDH) has gained attention because of its strong association with progression and early detection of breast cancer [20]. Serum LDH catalyzes the reversible conversion of pyruvate to lactate, playing a crucial role in anaerobic metabolism and maintaining levels of nicotinamide adenine dinucleotide (NAD+) for glycolysis [21]. It is found in the heart and muscle tissues and exhibits high activity and stability, making it a central enzyme in the glycolytic pathway and a potential therapeutic target [22]. Elevated serum LDH levels are observed in a variety of disorders, such as cardiac, hepatic, skeletal muscle, and renal diseases as well as leukemia [23–25]. In cancer, high serum LDH levels reflect altered metabolism that supports tumor growth and metastasis, establishing its value as a diagnostic and prognostic biomarker [23,26].

Lactate dehydrogenase is an enzyme that catalyzes the reversible conversion of pyruvate to lactate, playing a key role in maintaining levels of NAD+ for glycolysis. In cancer cells, LDH contributes to the "Warburg effect," a metabolic shift where glucose is preferentially metabolized to lactate even in the presence of oxygen, supporting rapid tumor growth and survival [27–31]. Mitochondrial dysfunction in tumor cells leads to increased membrane permeability and the release of intracellular enzymes, including LDH, which correlates with abnormal apoptotic signaling [32,33]. Elevated serum LDH levels in serum thus reflect altered cellular metabolism and progression of

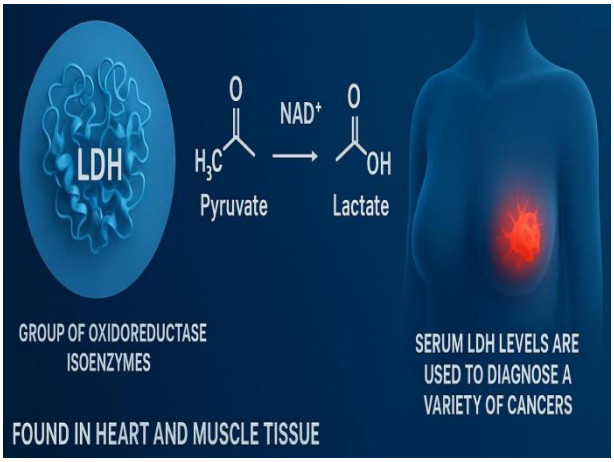

Figure (2): The reaction catalyzed by lactate dehydrogenase (LDH).

tumor, highlighting its value as a diagnostic and prognostic biomarker in breast cancer.

2. Materials and Methods

2.1. Study subjects

This cross-sectional study included 150 Iraqi women, aged 25–60 years, who were divided into two groups. The first group, the control group, included 50 women with no history of cancer or any other chronic disease. The second group included 100 women diagnosed with breast cancer, and were enrolled at the beginning of their chemotherapy and before undergoing radiotherapy. Diagnosis was confirmed through medical record review. Patients with chronic diseases, such as diabetes mellitus, hypertension, ischemic heart disease, and thyroid disorders, as well as smokers or alcohol consumers, were excluded from the study. Verbal informed consent was obtained from all participants prior to sample collection, and the study was approved by the Ethics Committee of the Al Amal National Cancer Hospital, Medical City, Baghdad, Iraq.

2.2. Specimen collection and preparation

Sample collection was approved by the management of Al Amal National Cancer Hospital, Baghdad, Iraq, under the direction of Dr. Mussab Kadhim Al-Aboodi. Blood samples (5 mL) were collected from each participant and placed in gel tubes. Samples from breast cancer patients were collected at different time points relative to chemotherapy, such as prior to starting of chemotherapy, after the first session, and after two to three sessions. Tubes were kept at room temperature until coagulation, and then centrifuged at 3,000 rpm for 15 min. The resulting sera were transferred into Eppendorf tubes and stored at low temperatures until analysis.

All biochemical analyses, such as LDH, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), prolactin (PRL), electrolytes, and kidney function tests, were performed using automated analyzers available in the hospital laboratory. Data distribution was tested using Shapiro–Wilk and Kolmogorov–Smirnov tests, and multifactorial analysis was used to control for potential confounding variables, such as age, disease stage, and treatment type. Statistical significance was set at $P < 0.05$.

2.3. Statistical analysis

All statistical analyses were performed using GraphPad Prism version 8.0.2. Data distribution was first tested for normality using Shapiro–Wilk and Kolmogorov–Smirnov tests. Continuous variables were presented as mean ± standard deviation (SD). The unpaired *t*-test was used to compare normally distributed data between the study groups. Multifactorial analysis was applied to control potential confounding variables, viz. age, disease stage, and treatment type. Differences with $P < 0.05$ were considered statistically significant [34].

3. Results and Discussion

3.1. Evaluation of serum lactate dehydrogenase

Lactate dehydrogenase enzyme plays an important role in glycolysis by converting pyruvate to lactate at the end of this process. The release of high levels of serum LDH into the blood is related to several diseases, such as cancers causes destruction the tissue [35]. The serum LDH levels in postoperative patients of breast cancer and controls are shown in Table 1 and Figure 5, which explained that the serum LDH levels in cancer patients were significantly high (352.28 ± 67.4) with $P < 0.0001$, compared to controls (120 ± 27.34). The LDH activity in breast cancer patients was higher, compared to that in controls, and this could be due to increased cell growth and cell migration compared to normal cells. Additionally, cancer cells have high energy demands and rely on aerobic glycolysis (Warburg effect), mitochondrial dysfunction, increased cellular permeability, and chemotherapy-induced inflammation, all of which contribute to elevated LDH levels in the serum. The cancer cells require excess of energy so the LDH can be considered an alternative to meet metabolic and aerobic glycolytic needs of cancer cells. In breast cancer patients, higher levels of LDH activity can give a prognostic indicator for the early warning of metastasis or recurrence [36,37].

3.2. Evaluation of serum urea & creatinine levels

The urea cycle reactions are important for removing free ammonia by hepatic detoxification and expelling it through the urethra; hence, urea levels are particularly important in patients exposed to diseases or treatments that can impair kidney function [38]. In this work, both urea and creatinine levels were evaluated in breast cancer patients, and the results shown in Table 2 and Figure 6 illustrate significantly higher levels of urea in breast cancer patients (41.76 ± 5.76), compared to controls (20.2 ± 3.61, $P < 0.0001$).

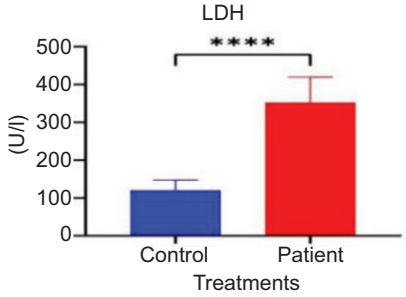

Figure (3): Activity levels of serum lactate dehydrogenase (LDH) in breast cancer patients and healthy controls.

Table (1): Serum LDH levels in breast cancer patients and healthy controls.

Group	LDH (mean ± SD)	*P* value
Controls	120 ± 27.34	<0.0001
Patients	352.28 ± 67.4	

Creatinine levels were also elevated (0.822 ± 0.16 in cancer patients vs. 0.506 ± 0.1 in controls, $P < 0.0001$).

The increase in urea levels in breast cancer patients may be attributed not only to tissue destruction and nucleic acid turnover but also to chemotherapy-induced renal stress, inflammation, and altered metabolism, which affect nitrogen balance. The levels of creatinine in serum play an important role in evaluating glomerular filtration rate and kidney function efficiency. Chemotherapeutic drugs can impair kidney function directly by damaging renal cells or indirectly through vascular and tubular effects, contributing to elevated serum urea and creatinine levels in cancer patients [39–41].

3.3. Evaluation of liver enzymes in serum (AST, ALT, and ALP)

Both serum AST and serum ALT, in addition to (ALP), were evaluated in breast cancer patients and healthy controls, and the results are shown in Table 3 and Figure 7. ALP is a nonspecific enzyme involved in hydrolyzing phosphate in alkaline medium, with activity reflecting presence of isoenzymes in the bone, liver, kidney, and intestinal lining [42]. ALT and AST are liver-related enzymes, and their serum levels increase in various diseases, including liver damage, viral hepatitis, myocardial infarction, bile duct obstruction, acute pancreatitis, and anemia [43].

The levels of ALP in cancer patients (113.64 ± 49.50, $P = 0.0630$) did not show a statistically significant difference, compared to controls (82.1 ± 22.3), suggesting that early-stage breast cancer or non-hepatic factors may not markedly affect ALP levels. Increase in ALP is generally observed in advanced stages of breast cancer and may serve to distinguish between stages or indicate metastasis [44,45].

The ALT activity was significantly higher in breast cancer patients (61.68 ± 30.5), compared to controls (18.1 ± 4.4, $P < 0.0001$), and AST was also elevated (39.52 ± 22.5 vs. 20.6 ± 5.6, $P = 0.0140$). Both ALT and AST catalyze the conversion of alanine to pyruvate and aspartate to oxaloacetate, respectively, and elevated levels reflect liver stress or damage, which may be secondary to tumor invasion, chemotherapy effects, or systemic inflammation. Previous studies report higher ALT and AST in malignant versus benign breast cancer patients, supporting their use as indicators of compromise of liver and renal functioning in progression of cancer [46].

3.4. Evaluation of serum electrolyte levels (Na^+, K^+, and Cl^-)

Kidney dysfunction is widely common in patients with malignant cancer because chemotherapy and other treatments can impair renal function, cause electrolyte disturbances, and induce immune deficiency [47]. However, many factors affect electrolyte levels, so identifying the causes is not straightforward [48].

Electrolyte levels were assessed in breast cancer patients and compared to healthy controls (Table 4 and Figure 8). Sodium levels did not differ significantly in cancer patients (142.7 ± 6.5, $P = 0.0663$), compared to controls (138.62 ± 3.4), suggesting that homeostatic mechanisms may maintain serum sodium despite renal stress or chemotherapy.

On the other hand, chloride levels were significantly higher in cancer patients (113.1 ± 4.5, $P < 0.0001$), compared to controls (103.28 ± 2.9). Potassium, which plays a key role in muscle excitability and nerve functioning, was also elevated in cancer patients (4.36 ± 0.55, $P = 0.0212$), compared to controls (3.92 ± 0.25). This may result from the release of intracellular contents from damaged tumor cells, chemotherapy-induced renal impairment, or altered hormonal regulation associated with cancer.

Serum electrolyte imbalance is clinically important for monitoring breast cancer patients, helping to assess renal injury, nephrotoxicity, and the overall prognosis. They

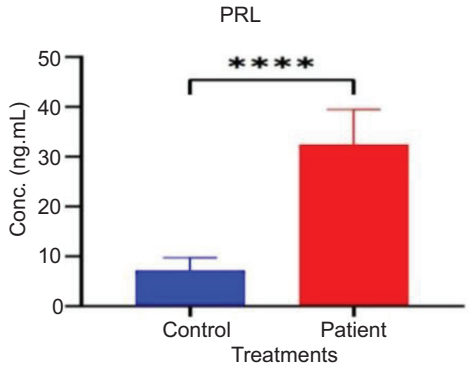

Figure (4): Serum levels of prolactin (PRL) in breast cancer patients and healthy controls.

Table (2): Serum levels of urea and creatinine in breast cancer patients and healthy controls.

Group	Urea (mean ± SD)	*P* value	Creatinine (mean ± SD)	*P* value
Controls	20.2 ± 3.61	<0.0001	0.506 ± 0.1	<0.0001
Patients	41.76 ± 5.76		0.822 ± 0.16	

Table (3): Serum levels of ALP, AST, and ALT in breast cancer patients and healthy controls.

Parameters	Mean ± SD		
	Controls	Patients	*P* value
ALP (U/L)	82.1 ± 22.3	113.64 ± 49.50	0.0630
Serum AST (U/L)	20.6 ± 5.6	39.52 ± 22.5	0.0140
Serum ALT (U/L)	18.1 ± 4.4	61.68 ± 30.5	<0.0001

Table (4): Serum levels of electrolytes in breast cancer patients and healthy controls.

Parameters	Mean ± SD		
	Controls	Patients	*P* value
Na^+	138.62 ± 3.4	142.7 ± 6.5	0.0663
K^+	3.92 ± 0.25	4.36 ± 0.55	0.0212
Cl^-	103.28 ± 2.9	113.1 ± 4.5	<0.0001

may also reflect systemic effects of tumor metabolism and treatment-related stress [49,50].

3.5. Evaluation of serum prolactin levels

Imbalance in hormone levels is associated with the development of various diseases. Recently, studies have focused on serum PRL in the prognosis of breast cancer. Many studies have shown a possible relationship between breast cancer and PRL hormone. PRL has cytokine-like properties; its receptor binds to the cell surface and cytoplasm, activating the Jak2/Stat5 signaling pathway [51,52].

Table 5 and Figure 9 show that breast cancer patients had significantly higher PRL levels (32.45 ± 7.0, $P < 0.0001$), compared to controls (7.186 ± 2.5). Elevated PRL may increase the risk of breast cancer, potentially by promoting cell division, reducing apoptosis, and contributing

Table (5): Serum levels of prolactin (PRL) in breast cancer patients and healthy controls.

Group	Prolactin (mean ± SD)	*P* value
Controls	7.186 ± 2.5	<0.0001
Patients	32.45 ± 7.0	

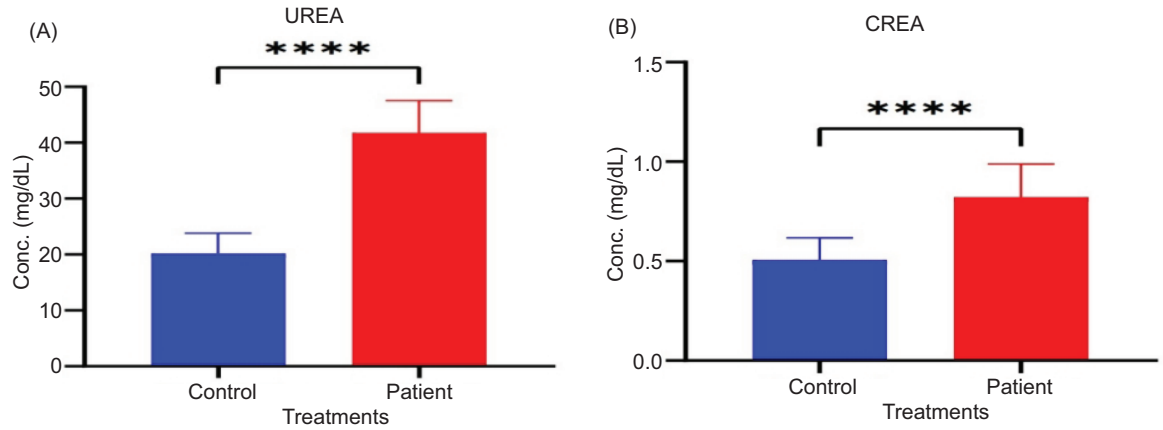

Figure (5): (A) Serum levels of urea in breast cancer patients and healthy controls; (B) Serum levels of creatinine in breast cancer patients and healthy controls.

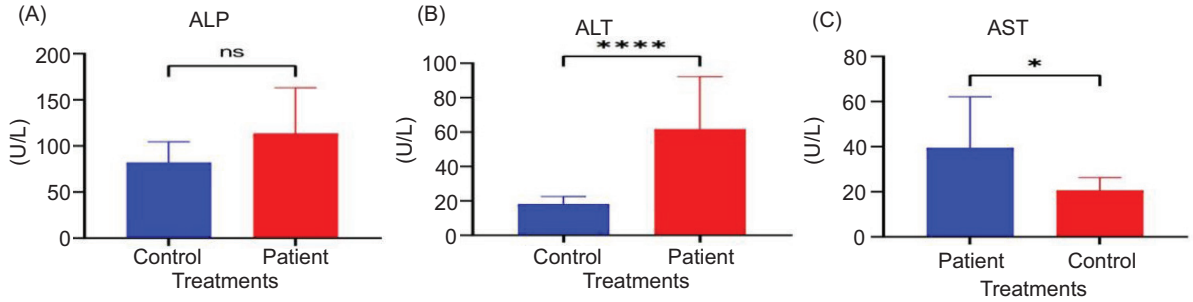

Figure (6): (A) Serum levels of ALP in breast cancer patients and healthy controls; (B) Serum levels of ALT in breast cancer patients and healthy controls; (C) Serum levels of AST in breast cancer patients and healthy controls.

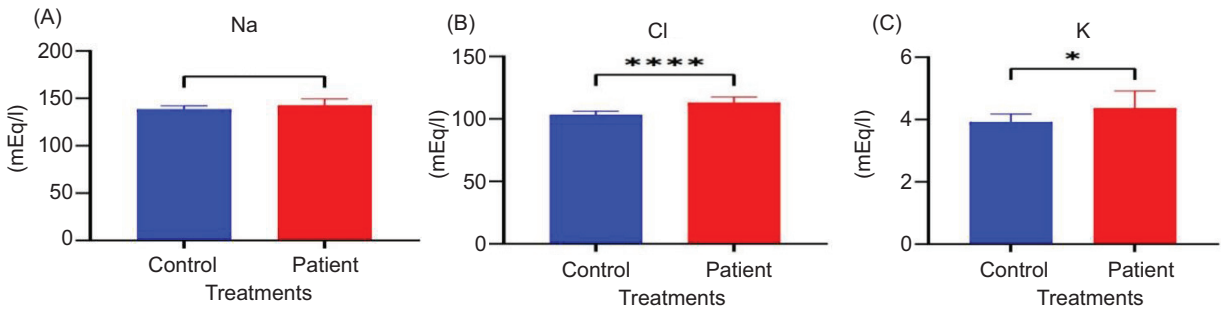

Figure (7): (A) Serum levels of Na^+ in breast cancer patients and healthy control; (B) Serum levels of Cl^- in breast cancer patients and healthy controls; (C) Serum levels of K^+ in breast cancer patients and healthy controls.

to resistance to cytotoxic drugs, although the exact mechanism remains unclear [53].

4. Conclusions

This study evaluates the levels of serum LDH in patients with breast cancer at different stages of chemotherapy, and demonstrates that LDH activity in cancer patients is higher, compared to that in controls. This can be due to increased cell growth and migration of cancer cells, compared to normal cells. Cancer cells require excess energy, so serum LDH serves as an alternative to meet the metabolic and aerobic glycolytic needs of cancer cells. In breast cancer patients, the higher levels of LDH activity can serve as a prognostic indicator for early warning of metastasis or recurrence. Additionally, it can be used for monitoring cancer progression and response to treatment.

Finally, this study demonstrates that elevated serum LDH levels are significantly associated with breast cancer and its progression. Serum LDH can serve as a valuable biomarker for prognosis, early detection of metastasis, and monitoring of therapeutic response, highlighting its potential role in clinical management of breast cancer patients.

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Conflict of Interest

The authors declared no conflict of interest.

Author Contributions (CRediT Taxonomy)

Contributor Role	Degree of Contribution		
	Lead	Equal	Supporting
Conceptualization		X	
Data curation		X	
Formal analysis		X	
Funding acquisition		X	
Investigation		X	
Methodology		X	
Project administration		X	
Resources		X	
Software		X	
Supervision		X	
Validation		X	
Visualization		X	
Writing-original draft		X	
Writing-review & editing		X	

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