



## Lactate dehydrogenase (LDH) and evaluation of response to breast cancer chemotherapy

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### ABSTRACT

Breast cancer is the leading cause of cancer death in women worldwide. The aim of this study was to determine the value of post-therapy serum LDH in assessing response at the completion of chemotherapy in breast cancer patients. This was a prospective cross-sectional study with data collection from May 2019 to November 2020, at the University Hospital of Bogodogo and at the SANDOF Polyclinic. We performed the LDH assay on serum from patients at the end of breast cancer chemotherapy who were at least 18 years old. Thirty (30) patients were included, with a mean age of  $47.47 \pm 2.10$  years. Based on RECIST criteria, 46.67% had a successful response to chemotherapy, while 53.33% had a poor response. The mean post-therapy serum LDH was  $256.15 \pm 25.99$  U/L and 46.67% of patients had elevated serum LDH. Mean serum LDH was significantly higher in patients with a personal history of breast cancer ( $p=0.0198$ ), increased CA 15-3 ( $p=0.0489$ ) and poor response to chemotherapy ( $p=0.0291$ ). Serum LDH was significantly higher in patients with a poor response to chemotherapy. Further studies are required to establish a more reliable correlation between serum LDH levels and response to breast cancer chemotherapy.

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**Keywords:** Lactate dehydrogenase, LDH, breast cancer, chemotherapy, treatment response, post-therapy.

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## INTRODUCTION

With 2,261,419 cases in 2020, breast cancer is the most common cancer in the world. It is the leading cause of cancer death in women, with 684,996 deaths in 2020. About one in four cancers diagnosed in women is breast cancer (Sung *et al.*, 2021). It is a heterogeneous disease with different clinical and biological characteristics, of which DNA modifications are a fundamental cause (Jaryum *et al.*, 2008). Nowadays, the TNM staging system is widely used for cancer prognosis. However, the survival of breast cancer patients after chemotherapy varies considerably, even within the same stages (Lai *et al.*, 2018). Furthermore, although significant progress has been made in management strategies, the clinical outcome of breast cancer patients remains unsatisfactory due to recurrence, metastasis or resistance to treatment (Badal *et al.*, 2021; Courtney *et al.*, 2022).

Therefore, it is essential to identify tumour and patient factors that predict aggressive biological behaviour and resistance to treatment. This identification of factors related to aggressive phenotypes and prognosis of breast cancer is essential for disease monitoring and accurate therapy. Clinico-pathological factors such as patient age, menopausal status, tumour size, lymph node status, tumour grade, progesterone oestrogen receptor, epidermal growth factor 2 (HER-2) and Ki-67 expression parameters have been developed to make a treatment plan (Esbah and Oksuzoglu, 2017). More recently, many studies have evaluated new serum biomarkers as prognostic factors in breast cancer, such as inflammatory factors, circulating microRNAs, exosomes, circulating tumour DNA and circulating tumour cells (Chedid *et al.*, 2022; Hua *et al.*, 2022; Yildiz *et al.*, 2022).

We now recognize that cancer cells have a different metabolism from normal cells, which gives them a selective advantage for proliferation and survival. Indeed, these cells preferentially metabolize glucose by glycolysis to generate energy even in the presence of adequate oxygen (Farhadi *et al.*, 2022). The use of lactate as an energy source requires the conversion of lactate to pyruvate

as well as the transport of lactate into and out of tumour cells by specific transporters. Lactate dehydrogenase (LDH), the most important metabolic enzyme of glycolysis, regulates the first pathway, catalyzing the conversion of pyruvate to lactate, with concomitant conversion of NADH and NAD<sup>+</sup>. It occurs in homo- or heterotetrameric forms, which are composed of M and H protein subunits encoded by the LDHA and LDHB genes respectively. Expression of LDHA and increased levels of LDH, particularly type 5 (LDH-5), are common events in highly invasive hypoxic cancers resistant to chemotherapy and radiotherapy (Zhou *et al.*, 2010; Ding *et al.*, 2017; S. Wang *et al.*, 2021). Increased levels of LDH are released into the bloodstream because of massive cell death and are associated with neoplastic disease because of tissue destruction caused by tumour growth.

Biochemical markers of tumour burden, including LDH, have been incorporated into several prognostic and staging scores for breast cancer (Zhang *et al.*, 2021; Ma *et al.*, 2022). Several studies have investigated the prognostic value of serum LDH in breast cancer patients. However, it is still difficult to confirm the prognostic role of serum LDH in breast cancer due to the conflicting results observed in the studies. Indeed, some studies have suggested that serum LDH is associated with a poor prognosis in breast cancer, while other studies have failed to demonstrate such correlations (Er *et al.*, 2008; Petekkaya *et al.*, 2014; Pelizzari *et al.*, 2019; Ma *et al.*, 2022). In addition, most studies focused on pre-therapeutic LDH (Petekkaya *et al.*, 2014; Ding *et al.*, 2017; Pelizzari *et al.*, 2019; S. Wang *et al.*, 2021). Thus, we conducted this study on post-therapy serum LDH to determine its value in assessing response at the end of chemotherapy in breast cancer patients.

## MATERIALS AND METHODS

### Materials

This was a prospective cross-sectional study with descriptive and analytical aims, with data collected from May 2019 to November 2020. We recruited patients at the Bogodogo University Hospital and the

SANDOF polyclinic, two health facilities located in the city of Ouagadougou in Burkina Faso. We performed the serum LDH assay in the biochemistry unit of the Charles de Gaulle University Hospital, in Ouagadougou (Burkina Faso).

The study was approved by the institutional ethics committee of the CERBA of Saint Camille (Pietro Annigoni Biomolecular Research Centre), reference N° 2020/II-03-016. Authorisation for data collection was obtained from the management of each collection center. All patients in the study gave their free and informed consent to participate in the study. Confidentiality of data was maintained throughout the study.

We sampled whole blood in dry tubes and centrifuged at 3500 rpm for 5 minutes. Two aliquots of serum per patient were prepared and stored at - 80°C until assays.

## Methods

Sampling was exhaustive during the study period. We included patients aged at least 18 years with a pathological diagnosis of breast cancer who had received chemotherapy. In a previous study, we described the data collection (Soudre et al., 2021). Thus, socio-demographic characteristics were obtained by interviewing the patients. Clinical, histological and biological data have been extracted from patients' records, consultation and hospitalization registers.

RECIST criteria (Dubreuil et al., 2017) and tumour markers (CA 15-3 and CEA) were used to assess the response of patients to chemotherapy. We distinguished between a good tumour response in patients with complete or partial remission and a poor tumour response when the patient was in stabilisation or progression.

For the assay of serum LDH, we used the IFCC-kinetic method with the Selectra Pro M chemical auto-analyser and reagents supplied by the ELITech Group (Reference LDH-L SL LLSL-0230). The normal values used according to the manufacturer's standards were 125-220 U/L.

## Statistical analysis

All study data were entered in Excel and analysed using Stata version 13.0. The Student's T-test was used to compare the means between the different groups. Statistical tests were considered significant when p was less than 0.05.

## RESULTS

### Socio-demographic characteristics

In the study, thirty (30) patients were included and their socio-demographic characteristics are presented in Table 1. The mean age of the patients was  $47.47 \pm 2.10$  years. The age group 18-45 years was the most represented (53.33%). The mean body mass index (BMI) was  $27.29 \pm 1.09$  kg/m<sup>2</sup>, with 63.33% of the patients being overweight or obese. Two patients (6.67%) had a personal history of breast cancer and four (13.33%) a family history of breast cancer.

### Clinical and paraclinical characteristics

Table 2 presented clinical and paraclinical characteristics of the patients. Tumour location on the right breast was the most frequent with 18 patients (60%) and the majority of tumours were large T4 (43.34%). Metastases, mainly bone, were present in 36.67%. The histological grade SBRm II (90%) and the histological type of non-specific infiltrating carcinoma (90%) were the most common. Of the patients, 50% and 16.67% had elevated post-treatment CA 15-3 and CEA respectively. The mean CA 15-3 value was  $165.75 \pm 76.50$  U/mL and  $16.14 \pm 10.90$  ng/L for CEA after chemotherapy.

### Chemotherapy characteristics

The majority of patients (70%) were on first-line chemotherapy; while nine patients (30%) were on at least their second line. Fourteen patients (46.67%) had a satisfactory response to chemotherapy according to RECIST criteria, while sixteen (53.33%) had a poor response.

### Post-treatment serum lactate dehydrogenase

The mean post-treatment serum LDH was  $256.15 \pm 25.99$  U/L. Of the patients,

53.33% (16/30) had normal LDH and 46.67% (14/30) had high serum LDH.

Tables 3 and 4 presented the determination of socio-demographic, clinical or paraclinical factors associated with the variation of post-therapy serum LDH.

Mean serum LDH was significantly higher in patients with a personal history of breast cancer ( $p=0.0198$ ). Similarly, the group of patients with increased CA 15-3 also had an elevated LDH ( $p=0.0489$ ). LDH was statistically higher in patients with a poor response to chemotherapy ( $p=0.0291$ ).

**Table 1:** Distribution of patients by socio-demographic characteristics.

Parameters	Characteristics	Number	Percentage (%)
Age (years)	≤ 45	16	53.33
	> 45	14	46.67
Body Mass Index	Normal	11	36.67
	High	19	63.33
Personal history of breast cancer	Yes	2	6.67
	No	28	93.33
Family history of breast cancer	Yes	4	13.33
	No	26	86.67

**Table 2:** Distribution of patients by clinical and paraclinical characteristics.

Parameters	Characteristics	Number (n=30)	Percentage (%)
Tumour site	Right breast	18	60.00
	Left breast	10	33.33
	Bilateral	2	6.67
Tumour size (T)	T2/T3	8	26.66
	T4	13	43.34
	Tx	9	30.00
Number of lymph nodes (N)	N0	3	10.00
	N1	17	56.67
	N2/N3	2	6.66
	Nx	8	26.67
Metastases (M)	M0	19	63.33
	M1	11	36.67
SBRm	II	27	90.00
	III	3	10.00
Histological type	NSIC*	27	90.00
	DCIS <sup>†</sup>	2	6.67
	LIC <sup>‡</sup>	1	3.33
Post-therapy CEA	Normal	25	83.33
	High	5	16.67
Post-therapy CA 15-3	Normal	15	50.00
	High	15	50.00

\* Non-specific invasive carcinoma <sup>†</sup>Ductal carcinoma in situ <sup>‡</sup>Lobular invasive carcinoma.

**Table 3:** Variations in post-therapy serum LDH by patient socio-demographic characteristics.

Parameters	Characteristics	LDH	
		Mean U/L	p-value
Age (years)	≤ 45	273.24±33.92	0.492
	> 45	236.62±40.72	
Body Mass Index	Normal	295.48±45.48	0.2567
	High	233.38±31.23	
Personal history of breast cancer	Yes	454.08±287.38	0.0198
	No	242.01±21.17	
Family history of breast cancer	Yes	187.99±37.79	0.3120
	No	266.64±29.07	

**Table 4:** Variations in post-therapy serum LDH by clinical, paraclinical and chemotherapeutic characteristics.

Parameters	Characteristics	LDH	
		Mean U/mL	p-value
Cancer site	Unilateral	256.22±27.53	0.9918
	Bilateral	255.12±86.77	
Tumour size (T)	T2/T3	304.06±59.56	0.2738
	T4/Tx	238.73±28.08	
Adenopathies (N)	N0/Nx	249.74±47.12	0.8550
	N1/N2/N3	259.86±31.67	
Metastases (M)	M0	247.63±29.92	0.6744
	M1	270.86±50.26	
SBRm	II	260.18±28.73	0.6503
	III	219.92±26.08	
Histological type	NSIC*	259.96±28.74	0.6679
	Others	221.86±25.70	
Post-therapy CA 15-3	Normal	213.04±13.23	<b>0.0489</b>
	High	299.26± 48.57	
Post-therapy CEA	Normal	243.54±25.06	0.2857
	High	319.21±96.73	
Chemotherapy line	1 <sup>st</sup> line	260.84±25.22	0.7881
	Several lines	245.20± 66.59	
Response to chemotherapy	Satisfactory	203.81±15.08	<b>0.0291</b>
	Poor	301.95±44.47	

\* Non-specific invasive carcinoma.

## DISCUSSION

The aim of the study was to determine the value of serum LDH in the evaluation of response to chemotherapy in breast cancer patients. The main limitation of the study is the small sample size, largely due to the selectivity of the criteria. In addition, the costs associated with the management of breast cancer remain out of reach for many patients (Tah-Monunde et al., 2020). Overall, thirty patients were included, with a mean age of  $47.47 \pm 2.10$  years.

Breast cancer is the most common tumour in women worldwide and is responsible for thousands of deaths each year (Sung et al., 2021). Disease incidence is increasing at all ages, while mortality is decreasing due to improved screening programmes and treatment. It is a heterogeneous disease, so treatment and prognosis depend on tumour subtype, grade, lymph node status and stage of disease. However, even patients with similar prognostic features may have different clinical outcomes. For this reason, a great deal of effort needs to be put into research into new prognostic factors. The identification of new prognostic factors is crucial for the improvement of breast cancer management and molecular and immunohistochemical studies are important. It is also important to consider costs, as only methods that are affordable for the majority of countries will have a wide enough distribution to have an impact on clinical outcomes for women with breast cancer worldwide. The knowledge of new prognostic factors over time has led to improved treatments for both primary and metastatic breast cancer, and consequently to improved survival. CA-15-3 and CEA antigens are the most widely used serum markers in breast cancer prognosis (Ebeling et al., 2002; Li et al., 2014). Determination of these markers allows monitoring of response

to treatment and early detection of recurrence or metastasis. Despite their lack of sensitivity and the many controversies surrounding their use, tumour markers, including CA 15-3, can be used to assess the response to treatment in patients (Soudre et al., 2021).

In the study, the mean post-therapy serum LDH was  $256.15 \pm 25.99$  U/L, above the retained normal value. LDH, an enzyme required for anaerobic glycolysis, is one of the biochemical markers of breast cancer. It is cheap, readily available and easy to estimate. Serum LDH is a key enzyme in the glucose metabolism pathway and catalyses the conversion of glucose to lactic acid (Gallo et al., 2015). In addition to its role in the regulation of cell metabolism, LDH is a well-known marker of tissue damage. Many pathological conditions, including cancer, show elevated LDH due to acute cell death or necrosis (Bidie et al., 2010; Barry et al., 2013). Indeed, one of its isoenzymes is increased in breast cancer due to the upregulation of its gene. It leads to increased serum LDH levels in breast cancer patients. In addition, high plasma LDH levels influence tumour progression and metastatic spread with a negative impact on outcomes in various types of cancer. Thus, LDH is associated with the prognosis of various cancers, including breast cancer, cervical cancer and lung cancer (Di Gioia et al., 2016; Gong et al., 2019; Wang et al., 2019).

In a meta-analysis of 76 studies in patients with several types of cancer, higher plasma LDH levels were associated with shorter progression-free survival and overall survival (Petrelli et al., 2015). Although the prognostic role of LDH in cancer is well established, the underlying biological mechanisms are still unclear and some possible explanations have been suggested. For example, high plasma LDH concentrations support anaerobic metabolism

during tumour growth and metastatic spread, producing energy requirements under hypoxic conditions (Hsu & Sabatini, 2008). Secondly, LDH exerts an inflammatory action on the tumour microenvironment, activating interleukins 23 and 17, and modulating arginase I activity. It inhibits the activation of CD8+ T cells and Natural Killers (NK), allowing cancer cells to escape the immune response (Ding et al., 2017). In addition, high levels of LDH promote tumour angiogenesis, cell migration and metastasis by inhibiting HIF-1 alpha degradation and increasing vascular endothelial growth factor production (Feng et al., 2018). Finally, preliminary evidence suggests that increased expression of LDHA and overproduction of lactate may also play a role in drug resistance (Apicella et al., 2018).

Pelizzari et al. (2019) examined the prognostic impact of plasma LDH levels on survival outcomes in patients with metastatic breast cancer during first-line treatment. Patients with elevated plasma LDH at inclusion who maintained high LDH levels after 12 weeks of first-line therapy had worse progression-free survival and overall survival than patients with stable normal LDH levels. Therefore, LDH could predict survival in patients with metastatic breast cancer and provided independent and dynamic prognostic information during first-line treatment. Based on their results, patients with stable high LDH levels or elevated LDH during first-line treatment could be monitored more frequently for disease progression, as they might have a shorter progression-free survival. Conversely, patients with stable normal LDH levels had prolonged progression-free survival and overall survival (Pelizzari et al., 2019).

In the study, mean serum LDH was significantly higher in patients with a personal history of breast cancer, suggesting that the presence of recurrence would be associated

with higher LDH levels. Agrawal et al. (2016) made similar findings in their study of pre- and postoperative markers in breast cancer patients, finding four patients with consistently elevated LDH levels who had recurrent disease. They concluded that higher serum LDH levels in these patients may be a warning sign of recurrence or metastasis.

Of the patients, 53.33% (n=16) had normal LDH and 46.67% (n=14) had high serum LDH. Furthermore, in our study, the group of patients with increased CA 15-3 also had elevated LDH. LDH was statistically higher in patients with a poor response to chemotherapy. The link between serum CA 15-3 values and prognosis, follow-up and therapeutic evaluation of breast cancer is now well established (Di Gioia et al., 2016; Soudre et al., 2021; Ma et al., 2022). Similarly, persistent elevation of serum LDH levels is due to poor response to treatment, metastasis or recurrence (Agrawal et al., 2016). Thus, the correlation of elevated LDH and CA 15-3 levels could confirm an insufficient response to treatment and thus a poorer prognosis in patients.

## **Conclusion**

Breast cancer is one of the leading causes of cancer mortality in women, which has now decreased due to advances in technology and new diagnostic and therapeutic methods. LDH, among many biochemical parameters, represents a very valuable enzyme in cancer patients with easy routine measurement possibility in many clinical laboratories. In our study, post-therapy serum LDH was significantly higher in patients with a poor response to chemotherapy. Studies with larger sample sizes and with pre- and post-treatment measurements may allow a better correlation between serum LDH levels and response to breast cancer chemotherapy.

## COMPETING INTERESTS

The authors declare that they have no competing interest.

## AUTHORS' CONTRIBUTIONS

Conceptualisation: FMS, JS, AB and AK. Data processing, formal analysis and software: FMS. Survey, methodology and project administration: FMS and JS. Supervision, validation and visualisation: EK and JS. Writing - original version: FMS. Drafting - revision and editing: AK, AK, RK, EK, JS and JS.

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