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Original Research Article

CORRELATIONAL EVALUATION OF SERUM LDH LEVELS WITH DIFFERENT TNM STAGING OF CARCINOMA BREAST: AN INSTITUTIONAL BASED STUDY

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ABSTRACT

Background: Breast cancer represents the most prevalent form of malignant neoplasm among women globally. High levels of LDH in serum are also measured during neoplastic diseases as a consequence of tissue destruction caused by the cancerous growth. Hence; the present study was conducted for correlational evaluation of serum LDH levels with different TNM staging of carcinoma breast.

Materials & Methods: A total of eighty cases of histopathologically confirmed breast carcinoma were included. Blood samples were obtained through venipuncture and collected in sterile plain blood vials. These samples were subsequently sent to the biochemistry laboratory, where serum LDH levels were measured spectrophotometrically using diagnostic kits at various time points, including preoperative and postoperative intervals. The results were documented in a Microsoft Excel spreadsheet and analyzed statistically using SPSS software. Diagnostic kits used for serum LDH: Cobas LDHI2 diagnostic kits by IFCC method. Serum LDH level at various intervals correlated with TNM stage of disease.

Results: Out of forty-two (52.5%) patients who were presented in stage III, 81% had high serum LDH value (>201U/L) and 19% had normal serum LDH value (100-200 U/L). In stage II patients mean value of serum LDH at preoperative period was higher than post operatively (257.36±87.76 Vs 230.42±53.97) but was not statistically significant. In stage III and IV follow up mean serum LDH was higher than preoperative levels, but it was not statistically significant.

Conclusion: Persistently high level of serum LDH or sudden increase in serum LDH level postoperatively may indicate poor outcome or metastasis. Higher levels of serum LDH in these patients may be an alarming warning sign of recurrence or metastasis. Also, in patients with efficacious treatment responses statistically significant reduction in serum LDH levels were seen in follow up. Thus, establishing prognostic value of serum LDH levels.

Key words: Lactate Dehydrogenase, Breast Cancer.

INTRODUCTION

Breast cancer represents the most prevalent form of malignant neoplasm among women globally. Patients diagnosed with breast cancer constitute approximately 36% of the total oncological population. In 2018, it was estimated that 2.089 million women received a breast cancer diagnosis. The incidence of this malignancy is on the rise across all global regions, with the highest rates

observed in industrialized nations. Nearly half of the worldwide cases are reported in developed countries.[1,2] This increasing trend is largely attributed to the so-called Western lifestyle, which is characterized by unhealthy dietary habits, tobacco use, high levels of stress, and insufficient physical activity. Mammography has emerged as the standard screening method for breast cancer, demonstrating its greatest efficacy in women aged 50 to 69 years. Traditional mammography exhibits a sensitivity range of 75% to 95% and a specificity between 80% and 95%. For women with a potential hereditary predisposition to breast cancer, magnetic resonance mammography is employed as an alternative screening modality. In instances where mammography reveals a suspicious lesion, further evaluation through ultrasound is conducted, and if warranted, a core needle biopsy is performed, followed by a histopathological assessment of the tumor.[3,4]

Despite the extensive research for many years throughout the world, the etiopathogenesis of cancer still remains obscure. For the early detection of carcinoma of various origins, a number of biochemical markers have been studied to evaluate the malignancy. However; no single marker has proved to be a sensitive and specific indicator of early malignancy.[5]

LDH is a 140kDa tetramer molecule that exists in five major isoenzymes, numbered LDH-1 through LDH-5, formed by the association of two different types of 35kDa subunits, M(muscle) and H(heart), encoded by LDHA and LDHB genes, respectively. Increased levels of this protein are in fact released in blood as a consequence of massive cell death and are associated with acute diseases. High levels of LDH in serum are also measured during neoplastic diseases as a consequence of tissue destruction caused by the cancerous growth. The prognostic value of serum LDH level in breast cancer patients has been investigated in several studies.[6-8] Hence; the present study was conducted for correlational evaluation of serum LDH levels with different TNM staging of carcinoma breast.

MATERIALS AND METHODS

A total of eighty cases of histopathologically confirmed breast carcinoma were included. The inclusion criteria specified that all participants had to be diagnosed with breast cancer and admitted to Maharana Bhupal Government Hospital in Udaipur, Rajasthan. Blood samples were obtained through venipuncture and collected in sterile plain blood vials. These samples were subsequently sent to the biochemistry laboratory, where serum LDH levels were measured spectrophotometrically using diagnostic kits at various time points, including preoperative and postoperative intervals. The results were documented in a Microsoft Excel spreadsheet and analyzed statistically using SPSS software. Diagnostic kits used for serum LDH: Cobas LDHI2 diagnostic kits by IFCC method. Normal value of serum LDH according to this method < 200 U/L. Minimum and maximum value of serum LDH was estimated and different slabs of serum LDH was formed with range of 100 U/L. Mean value of serum LDH was calculated at preoperatively, postoperatively and postoperative follow up time. P value was calculated through a computer-generated software using the student's unpaired 't' test and paired 't' test. Serum LDH level at various intervals correlated with TNM stage of disease.

RESULTS

The age of females in the study was in the range of 26 to 80 years, with majority belonging to age group 51-60 years (33.75 %), followed by 30% of females between 41-50 years, about 16.2% of females presented between 31-40 years and 10% of females between age 61-70 years. Only a small population (5%) are presented at extremes of age (21-30 years and > 71 years). All the patients in this study had complaints of lump in the breast; next common complaint was lump in breast with pain. A large number of patients also presented with history of lump in breast with skin changes and retraction of nipple. Some patients also complained of discharge from nipple and weight loss. Most of the patients presented with a mass in the upper outer quadrant (n=41, 51.25%). Out of eighty, sixteen cases (20%) had involvement of multiple quadrants. Fifteen patients had mass in the upper inner quadrant; four patients had mass in the lower outer quadrant and four rest in the lower inner quadrant. At the time of the presentation, 7.5% of patients were in stage IV. All these patients had high serum LDH value (>201 U/L). Out of forty-two (52.5%) patients who presented in stage III, 81% had high serum LDH value (>201U/L) and 19% had normal serum LDH value (100-200 U/L). Out of thirty-two (40%) patients who presented with stage II, 78% had high serum LDH value (>201 U/L) and 22% had normal serum LDH value. Postoperatively, 7.5% patients were in stage IV. Out of these patients in stage IV, 83% had high serum LDH value (>201 U/L) and 17% had normal serum LDH value between 100-200 U/L. Forty-two (52.5%) out of 80 patients were in stage III, 62% of which had high serum LDH value (>201 U/L) and 38% had normal serum LDH value. Thirty-two (40%) out of 80 patients were in stage II, 72% of this proportion had high serum LDH value (>201 U/L) and 28% had normal serum LDH value. In stage II patients mean value of serum LDH at preoperative period was higher than post operatively (257.36±87.76 Vs 230.42±53.97) but was not statistically significant. In stage III patients mean value of serum LDH at preoperatively was significantly higher than post operatively (298.04±133.26 Vs 232.42±66.95, $p<0.05$). In stage IV patients mean value of serum LDH

preoperatively was significantly higher than postoperatively (431.47±111.419 Vs 320.76±96.396, p <0.05). In stage II patients mean value of serum LDH preoperatively was significantly higher than follow up levels (257.36±87.76 Vs 201.21±72.0, p<0.005). In stage III and IV follow up mean serum LDH was higher than preoperative levels, but it was not statistically significant.

Table 1: Quadrant of breast involved in breast carcinoma patients

Quadrant of breast	No. of cases	Percentage (%)
Upper outer quadrant	41	51.25
Upper inner quadrant	15	18.75
Lower outer quadrant	04	5
Lower inner quadrant	04	5
Multiple quadrant	16	20
Total	80	100

Table 2: Preoperative serum LDH slab correlated with stage of disease in carcinoma of breast patients

LDH	Stage I number (%)	Stage II number (%)	Stage III number (%)	Stage IV number (%)	Total number (%)
100-200 U/L	0(0)	9(11.25)	8(10)	0(0)	17(21.25)
201-300 U/L	0(0)	17(21.25)	23(28.75)	0(0)	40(50)
301-400 U/L	0(0)	3(3.75)	5(6.25)	2(2.5)	10(12.5)
>401 U/L	0(0)	3(3.75)	6(7.5)	4(5)	13(16.25)
Total	0(0)	32(40)	42(52.5)	6(7.5)	80(100%)

Table 3: Post-operative serum LDH slab correlated with stage of disease in carcinoma of breast patients

LDH	Stage I number (%)	Stage II number (%)	Stage III number (%)	Stage IV number (%)	Total number (%)
100-200 U/L	0(0)	9(11.25)	16(20)	1(1.25)	26(32.5)
201-300 U/L	0(0)	20(25)	21(26.25)	2(1.25)	43(53.75)
301-400 U/L	0(0)	3(5)	4(5)	2(2.5)	9(11.25)
>401 U/L	0(0)	0(0)	1(1.25)	1(1.25)	2(2.5)
Total	0(0)	32(40)	42(52.5)	6(7.5)	80(100%)

Table 4: Mean value of serum LDH correlated with different TNM stages at different timeline points

Stages	Preoperatively LDH (U/L) (a)	Postoperatively LDH (U/L) (b)	Follow up LDH (U/L) (c)	P value* (a vs b)	P valve* (a vs c)
Stage I	---	---	--	--	--
Stage II	257.36±87.76	230.42±53.97	201.21±72.0	0.095	**0.008**
Stage III	298.04±133.26	232.42±66.95	319.45±158.53	**0.002**	0.412
Stage IV	431.47±111.419	320.76±96.396	545.49±318.49	**0.004**	0.540

*P value was calculated by student's paired 't' test

DISCUSSIONS

The incidence of breast cancer is increasing worldwide due to the continuous growth of the population and the ageing of the population. The highest incidence rates are recorded in developed countries. For the early detection of carcinoma of various origins, a number of biochemical markers have been studied. However, no marker specific for breast cancer has been discovered and those currently available lack the sensitivity and specificity for early detection of the disease or for determining the tumour burden. Other biochemical markers available in the market for screening, confirming diagnosis, staging, monitoring treatment and prognosis are expensive and increase the overall cost of the treatment. Many methods of diagnosing carcinoma breast have been available like the ultrasonography, fine needle aspiration cytology (FNAC), mammography, excisional biopsy, trucut biopsy, etc. However, many of these methods are unapproachable for the general population as the facilities for the these are available only at sophisticated and well-equipped center with new latest technology. There is, therefore need of simple biochemical investigation, which can be easily assayed and are less expensive. Serum LDH is economical and easy to estimate. It does not require sophisticated centre or any latest technology and can be performed even at rural centers.[9-12]

The age of females in the study was in the range of 26 to 80 years, with majority belonging to age group 51-60 years (33.75 %), followed by 30% of females between 41-50 years, about 16.2% of females presented between 31-40 years and 10% of females between age 61-70 years. Only a small population (5%) are presented at extremes of age (21-30 years and > 71 years). All the patients in this study had complaints of lump in the breast; next common complaint was lump in breast with pain. A large number of patients also presented with history of lump in breast with skin changes and retraction of nipple. Some patients also complained of discharge from nipple and weight loss. Most of the patients

presented with a mass in the upper outer quadrant (n=41, 51.25%). Out of eighty, sixteen cases (20%) had involvement of multiple quadrants. Fifteen patients had mass in the upper inner quadrant; four patients had mass in the lower outer quadrant and four rest in the lower inner quadrant. At the time of the presentation, 7.5% of patients were in stage IV. All these patients had high serum LDH value (>201 U/L). Out of forty-two (52.5%) patients who were presented in stage III, 81% had high serum LDH value (>201U/L) and 19% had normal serum LDH value (100-200 U/L). Out of thirty-two (40%) patients who presented with stage II, 78% had high serum LDH value (>201 U/L) and 22% had normal serum LDH value. Postoperatively, 7.5% patients were in stage IV. Out of these patients in stage IV, 83% had high serum LDH value (>201 U/L) and 17% had normal serum LDH value between 100-200 U/L. Forty-two (52.5%) out of 80 patients were in stage III, 62% of which had high serum LDH value (>201 U/L) and 38% had normal serum LDH value. Thirty-two (40%) out of 80 patients were in stage II, 72% of this proportion had high serum LDH value (>201 U/L) and 28% had normal serum LDH value. In stage II patients mean value of serum LDH at preoperative period was higher than post operatively (257.36±87.76 Vs 230.42±53.97) but was not statistically significant. Agrawal A et al evaluated the LDH levels in circulation of newly diagnosed patients of breast cancer and tried to correlate it with different TNM staging of carcinoma breast before interventions and after adjuvant therapy of these patients. Out of a total of 83 participants, 10 participants were having adverse events following surgery and the remaining 73 participants were without adverse events following surgery. The significant difference in serum LDH levels between two groups, with and without adverse surgical outcome was calculated by Mann-Whitney U test. Patients with higher clinical TNM staging were having higher serum LDH levels. The serum LDH levels in the sixth months following surgery showed a trend of statistically significant difference between patients with and without adverse events. As increased serum LDH levels in breast cancer patients show poor prognosis, surgical outcome or advanced metastases. Serum LDH monitoring can be used as a prognostic biomarker in patients of breast cancer.[13]

In stage III patients mean value of serum LDH at preoperatively was significantly higher than post operatively (298.04±133.26 Vs 232.42±66.95, $p<0.05$). In stage IV patients mean value of serum LDH preoperatively was significantly higher than postoperatively (431.47±111.419 Vs 320.76±96.396, $p <0.05$). In stage II patients mean value of serum LDH preoperatively was significantly higher than follow up levels (257.36±87.76 Vs 201.21±72.0, $p<0.005$). In stage III and IV follow up mean serum LDH was higher than preoperative levels, but it was not statistically significant. Jia Z et al, in a previous study, found that abnormal baseline LDH levels (> 250 IU/L) were significantly associated with age (> 40 y vs. ≤ 40 y, OR: 0.383, P = 0.031) and number of metastatic sites (2 vs. 1, OR: 4.619, P = 0.006; ≥ 3 vs. 1, OR: 4.727, P = 0.002). The progression-free survival (PFS) of patients with post-treatment LDH higher than baseline (Group 1) was significantly shorter than that in patients with LDH decreased to normal (Group 3) and those with normal baseline and post-treatment LDH (Group 4) (Group 3 vs. Group 1, HR: 0.517, P = 0.038; Group 4 vs. Group 1, HR: 0.346, P < 0.001). Overall survival (OS) in patients with abnormal baseline LDH was significantly shorter than in patients with normal baseline LDH (abnormal vs. normal, HR: 2.073, P < 0.001). Patients whose post-treatment LDH decreased to normal had the most objective response (complete and partial responses) rate after first-line chemotherapy (Group 3 vs. Group 1, OR: 0.074, P < 0.001). In this exploratory analysis, baseline LDH levels associated with OS, while LDH changes after first-line chemotherapy associated with PFS and the chemotherapeutic response. These results showed that LDH may have important prognostic value for the survival and chemotherapeutic response in patients with advanced TNBC.[14] Wu J et al retrospectively collected 198 hypopharyngeal cancer patients treated with surgery. Three-year and Five-year of disease-free survival (DFS, 67.0 vs. 57.4%, 65.8 vs. 39.8%, p = 0.007) and overall survival (OS, 74.8 vs. 68.9%, 66.8 vs. 50.8%, p = 0.006) exhibited significant differences between low LDH level and high LDH level groups. Univariate analysis showed that pretreatment elevated serum LDH served as an unfavorable determinant with regard to DFS and OS. Further multivariate analysis also confirmed that LDH was an independent predictor for DFS and OS. Additionally, N status and age were also found to be significantly associated with both DFS and OS. Pretreatment elevated serum LDH is an inferior prognostic factor for patients with hypopharyngeal cancer.[15]

CONCLUSION

The persistently high level of serum LDH or sudden increase in serum LDH level postoperatively may indicate poor outcome or metastasis. Higher levels of serum LDH in these patients may be an alarming warning sign of recurrence or metastasis. Also, in patients with efficacious treatment responses statistically significant reduction in serum LDH levels were seen in follow up. Thus, establishing prognostic value of serum LDH levels.

REFERENCES

1. Nardin S., Mora E., Varughese F.M., D'Avanzo F., Vachanaram A.R., Rossi V., Saggia C., Rubinelli S., Gennari A. Breast Cancer Survivorship, Quality of Life, and Late Toxicities. Front. Oncol. 2020; 16:864.

2. “Global Cancer Observatory” International Agency for Research on Cancer, Lyon, France. [(accessed on 1 June 2020)]. Available online: https://gco.iarc.fr/
3. Bellanger M., Zeinomar N., Tehranifar P., Terry M.B. Are Global Breast Cancer Incidence and Mortality Patterns Related to Country-Specific Economic Development and Prevention Strategies? J. Glob. Oncol. 2018; 4:1–16.
4. Elmore J.G., Armstrong K., Lehman C.D., Fletcher S.W. Screening for breast cancer. JAMA. 2005; 293:1245–1256.
5. Di Stefano G, Manerba M, Di Ianni L, Fiume L. Lactate dehydrogenase inhibition: exploring possible applications beyond cancer treatment. Future Med Chem. 2016;8(6):713–725.
6. Mishra S, Sharma DC, Sharma P. Studies of biochemical parameters in breast cancer with and without metastasis. Indian J Clin Biochem. 2004;19(1): 71–75
7. Khan N, Tyagi SP, Salahuddin A. Diagnostic and prognostic significance of serum cholinesterase and lactate dehydrogenase in breast cancer. Ind J Pathol Microbiol. 1991;34(2):126–30.
8. Radenkovic S, Milosevic Z, Konjevic G, Karadzic K, Rovcanin B, Buta M, et al. Lactate dehydrogenase, catalase, and superoxide dismutase in tumour tissue of breast cancer patients in respect to mammographic findings. Cell Biochem Biophys. 2013;66(2):287–95
9. Elston C.W., Ellis I.O. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology. 1991; 19:403–410.
10. Amin M.B., Greene F.L., Edge S.B., Compton C.C., Gershenwald J.E., Brookland R.K., Meyer L., Gress D.M., Byrd D.R., Winchester D.P. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA Cancer J. Clin. 2017; 67:93–99.
11. Hayes D.F., Isaacs C., Stearns V. Prognostic Factors in Breast Cancer: Current and NewPredictors of Metastasis. J. Mammary Gland Biol. Neoplasia. 2001; 6:375–392.
12. De Boer M., van Dijck J.A., Bult P., Borm G.F., Tjan-Heijnen V.C. Breast Cancer Prognosis and Occult Lymph Node Metastases, Isolated Tumor Cells, and Micrometastases. J. Natl. Cancer Inst. 2010; 102:410–425.
13. Agrawal A, Gandhe MB, Gupta D, Reddy MV. Preliminary Study on Serum Lactate Dehydrogenase (LDH)-Prognostic Biomarker in Carcinoma Breast. J Clin Diagn Res. 2016 Mar;10(3):BC06-8.
14. Jia Z, Zhang J, Wang Z, Wang B, Wang L, Cao J, Tao Z, Hu X. An explorative analysis of the prognostic value of lactate dehydrogenase for survival and the chemotherapeutic response in patients with advanced triple-negative breast cancer. Oncotarget. 2018 Jan 13;9(12):10714-10722.
15. Wu J, You K, Chen C, Zhong H, Jiang Y, Mo H, Song J, Qiu X, Liu Y. High Pretreatment LDH Predicts Poor Prognosis in Hypopharyngeal Cancer. Front Oncol. 2021 Mar 11; 11:641682.