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STUDY ON ROLE OF ALP, LDH AND LIPASE AS PROGNOSTIC MARKERS IN FEMALE BREAST CANCER PATIENTS OF SAURASTRA REGION OF GUJARAT

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ABSTRACT Breast cancer is the second most common malignancy related mortality observed in women worldwide. It is multifactorial in nature having many factors including genetics, lifestyle factors, socioeconomical etc. playing role in variable occurance and heterogeneity towards treatment. Routine diagnosis for breast cancer is usually done by mammography and histopathology, but recent adavnces suggests the role of certain biomarkers such as tumour specific hormones, serum proteins, serum enzymes etc as a supplementary parameters to predict overall prognosis of the patients. In the present study, relative analysis of the levels of ALP (alkaline phosphatase), LDH (lactate dehydrogenase) and Lipase enzyme is determined among breast cancer patients at the time of diagnosis using semi automated clinical biochemistry analyzer. further correlation is done with other socio-demographic factors prevalent among the patients. For this purpose, preoperative blood samples of breast cancer patients were collected from Rajkot Cancer Hospital and study concludes that higher expression of LDH was found in 50% of breast cancer patients, while 31.81% of breast cancer patients had higher expression levels of lipase and ALP enzyme among the study population.

KEYWORDS : Breast cancer, Serum enzymes, ALP (alkaline phosphatase), LDH (lactate dehydrogenase), Lipase.

INTRODUCTION

The second most common cause of death worldwide is cancer. Breast Cancer (BC) is a growing global concern and the leading cause of cancer mortality among women worldwide (Rebecca Dent *et al.,* 2007). Breast cancer is typically believed to represent different genetic changes and categorized into distinct molecular subtypes based on receptor status. One of the types is triple-negative breast cancer (TNBC), it is a heterogeneous clinical-pathological cancer that demonstrates a high risk of relapse and poor prognosis (Bo Chen *et al.,* 2016). Around 15 to 20 percent of women with breast cancer are TNBC type, were timely diagnosis can lead to good prognosis of the disease. In recent times many studies have focused on serum enzyme levels that could work as a diagnostic markers for breast cancer. The efficacy of these parameters in forecasting patient prognosis for TNBC has been verified by evidence from recent researches (Vijay Shrivastava *et al.,* 2016).

ALP, LDH and Lipase are an candidate serum enzymes on which fewer research are been conducted to rule out their usability as prognostic biomarker for breast cancer. ALP is a serum enzyme whose overall concentrations represent the combined action of many isoenzymes located in the lining of the liver, bone, kidney, and intestines. This skeletal isoenzyme is derived from osteoblasts and, as bone repair actions, for instance with bone metastases causes the release of significant quantities of the enzyme (Keshaviah *et al.,* 2007). This enzyme is found in almost all tissues in the human body but is primarily localized in the brain, liver, bile duct, kidney, and placenta (Ying Jin *et al.,* 2015). While in tissue cells, ALP is concentrated, blood levels of the enzyme are usually low. Nevertheless, the blood ALP level increases in certain conditions such as pregnancy, cancer, and bone metastasis (Mamari AS *et al.,* 2013). According to researchers, the localization of ALP in the nucleus suggests proliferation (Yamamoto K *et al.,* 2003). In the cancer cell nucleus, there is an increased activity of ALP (Xu XS *et al.,* 2015).

Several studies have recently shown that serum ALP levels have increased rapidly with tumor progression, and the blood level of ALP can be used as a biomarker for early detection of metastasis (Ling Z, 2013). Increased levels of serum ALP are correlated to poor prognosis in certain cancers (Wei XL *et al.,* 2016). Some researches have also shown that an elevated level of serum ALP has been reported in patients with breast cancer and has been frequently proven to indicate liver and bone metastases (Choudhari A *et al.,* 2013).

Second candidate enzyme is LDH, which is found in various tissues and can be detected in serum (Goldman RD *et al.,* 1994). Typically, the LDH blood levels are normal. However, the level of LDH increases due to tissue injuries or infection, for example, autoimmune disorders, degenerative conditions, inflammation, or cancers (Jin Y *et al.,* 2013). When the cells multiply more quickly, LDH is secreted at an accelerated rate into the bloodstream (Seth RK *et al.,* 2003). In cancer cells, LDH is a crucial enzyme in the energy production procedure; it catalyzes the conversion of pyruvate to lactate under hypoxic conditions, playing a significant role in the proliferation and survival of tumors. In different forms of cancer, the elevated LDH level was associated with shorter survival. The amount of LDH in the blood was associated with the tumor and was supposed to represent the proliferation and inflammatory capacity of the tumor (Suh SY *et al.,* 2007). ErbB2 (Her2/neu) is an oncogene, linked with a bad prognosis and responsible for PI3K / Akt activation, which contributes to LDH genes being stimulated and upregulated by HIF-1α, ultimately leads to high LDH levels in the blood (Zhao *et al*., 2009). Elevated blood LDH has been linked to higher hypoxia-related gene expression including HIF-1α, angiogenesis, and vascular endothelial growth factor (VEGF). Activation of LDHA and VEGF is also mediated throughout hypoxia by the HIF-1α transcriptional process (Azuma *et al.,* 2007). Many tumors have higher LDH levels than normal tissues and this has been known for a long time. In certain solid tumors, elevated LDH can also be used as a prognostic marker which is elevated in malignant tissue than in normal. (Jin Y *et al.,* 2013). In human breast cancer, the involvement of LDH associates with tumor prognosis. In contrast to normal breast tissue, metastatic breast cancer often experiences increased LDH levels (Kawamoto M, 2008). It is understood that LDH and lactate indicate the tumor size and tumor aggressive. The increased level of LDH induces reduce treatment responsiveness. LDH may also be considered as an indicator of tumor progression (Suh SY *et al.,* 2007).

Third enzyme as a study target is Lipase, which plays an important role in energy metabolism and the generation of secondary messengers. Cancer cells enhance the absorption of fatty acids through lipase-catalyzed triglyceride hydrolysis into fatty acids needed for the growth and survival of tumors (Nancy B. Kuemmerle *et al.,* 2011).

DNA microarray study has shown that lipase I expression in the Ewing tumor is considerably higher. Lysophosphatidic acid (LPA), an effective regulator of many tumor-related activities, such as cell transformation, proliferation, induction of apoptosis, induction of differentiation, and angiogenesis, is generated by LIPI enzymatic action (Rivera-Lopez CM *et al.,* 2008). Alpha-beta Hydrolase Domain Containing 2 (ABHD2) is a part of the lipase family enzyme. DNA microarray results from breast cancer studies exhibit elevated

production of ABHD2 relative to normal tissue (Finak G *et al.,* 2008). A part of the lipase superfamily known as lipoprotein lipase (Lipase D) has increased expression in brain tumors that allow them to have resistant towards apoptosis and it is linked with reduced survival in lung cancer (Trost Z *et al*., 2009). Lipase member H (LIPH) was found in the cytoplasm of breast cancer cells, and the expression of LIPH protein in breast cancer tissues was considerably increased. The increased level of LIPH proteins was correlated with a weak prognosis (Meizi Cui *et al.,* 2014). Increased production of endothelial lipase (LIPG) is likely to rise the accessibility of lipids needed for the development and regulation of breast cancer cells, thus promoting the progression and development of these cells, as well as tumor progression and metastasis (Felipe Slebe *et al.,* 2016).

No clear precise pathways were mediating the association between the expression of these enzymes and the prognosis of breast cancer. To determine it, additional research is needed. This study is focused on the use of serum levels of lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and lipase in breast cancer patients in early diagnosis and correlating the serum levels of these enzymes and breast cancer stage.

MATERIALS AND METHODS

In the current research, newly diagnosed and histologically confirmed primary breast cancer patients admitted to Rajkot Cancer Society Hospital for breast cancer surgery and therapy from December 2016 to May 2017 have been retrospectively reported. The blood samples from 24 newly diagnosed patients with breast cancer and 28 normal individuals were obtained.

A total of 52 individuals met the inclusion requirement. 95% of patients' data were collected prior to any surgical procedure such as mastectomy or traditional breast surgery. presence of infection, the involvement of haematological conditions, acute as well as chronic inflammatory or autoimmune diseases, previous treatment with steroids. are exclusion criteria for the study.

For each individual, a comprehensive health history was reported on a structured questionnaire developed and accepted for the study. History of the menstrual cycle, breastfeeding, past infection or inflammation, use of contraceptive pills, hormone drugs, previous operation, use of other conventional medicines, and family history of cancer, obesity, blood pressure, or diabetes-like illnesses have been recorded. It also reported addiction to smoking, consuming alcohol and chewing tobacco, and their geographic location.

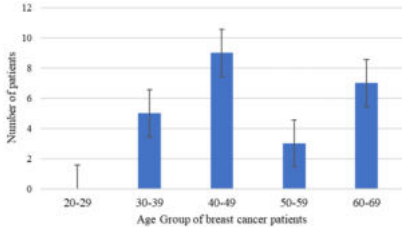
The blood samples of all the included individuals were obtained under the sterilized condition in a vaccinated EDTA tube with 20 percent EDTA as an anti-coagulant. Informed consent were taken from each subjects and they were also told that their samples would be used exclusively for research purposes and their confidentiality will be respected.

The samples were then subjected to LDH, ALP, and lipase analysis using a semi-automated analyzer on the same day of the sample collection. The Ethical Committee of the Hospital and the college approved this research work.

Microsoft Office Excel 2016 and Graphpad Prism 5 software were used for the statistical analysis and correlation of enzyme test results with sociodemographic and clinicopathological factors to analyze the overall health condition of study subjects.

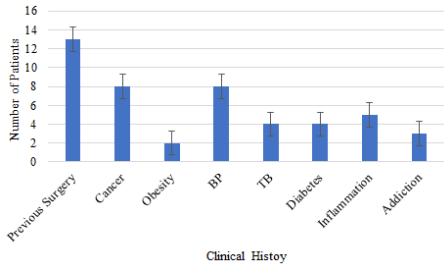
RESULTS

24 breast cancer patients were included in this study. 9 breast cancer patients were from the urban region and 15 were from the rural background. A high incidence rate of breast cancer in a rural area might be because of the lack of education, resources, and delayed admission to the hospital.



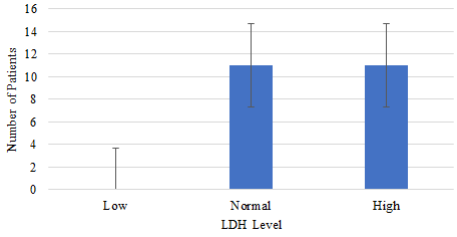
Graph 1. Age-wise distribution of breast cancer patients.

All the participants were divided into different age groups from 20 to 70 as seen in graph 1. The mean age of breast cancer patients was 48.88 ±11.91 years. The age group 40-49 years has the maximum number of breast cancer patients.



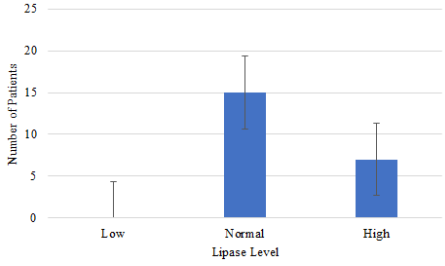
Graph 2. Clinical history of the breast cancer patients.

It is known that cancer is a complex disorder that involves multiple conditions resulted from multiple risk factors. During this study, patients' clinical history was analyzed to understand the role of risk factors in breast cancer occurance. 13 breast cancer patients had undergone either single or multiple surgeries. There were 8 patients with a family history of various cancers. Obesity was found out in 2 patients. 8 breast cancer patients had a family history of blood pressure. 4 patients were suffering from tuberculosis. Diabetic history was observed in 4 patients. Inflammation was found out in 5 patients. 3 patients had different addictions such as smoking, chewing tobacco.



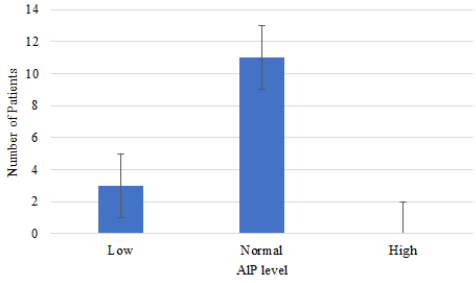
Graph 3. The LDH enzyme level in the breast cancer patients.

It can be seen in graph 3 that the LDH was measured for 22 breast cancer patients. The mean LDH expression level for breast cancer patients was 616.87±454.16 U/L. 11 patients had higher LDH value while the rest of the 11 had a normal level. Thus, higher expression of LDH was found in 50% of breast cancer patients.



Graph 4. The lipase enzyme level in the breast cancer patients.

As per graph 4, the lipase was measured for 22 breast cancer patients. The mean lipase expression level for breast cancer patients was 65.81±51.69 U/L. 7 patients had higher lipase value while the rest of the 15 had a normal level. Thus, 31.81% of breast cancer patients had higher expression levels of lipase enzyme.



Graph 5. The ALP enzyme level in the breast cancer patients.

The ALP was measured for 14 breast cancer patients as seen in graph 5. The mean ALP expression level for breast cancer patients was 55.76±17.42 U/L. 3 patients had low ALP value while the rest of the 11 had a normal level. Thus, 31.81% of breast cancer patients had higher expression levels for ALP.

DISCUSSION

The malignancy of breast cells results in breast cancer. The malignant cells emerge inside the lining of the milk glands or breast ducts and cause breast cancer. Metastatic breast cancer is more aggressive and proliferative than other forms of breast cancer. Out of the total death due to breast cancer, metastatic breast cancer is the most common cause and responsible for around 500,000 deaths per year worldwide (Musa Mayer, 2010).

A study conducted on breast cancer patients by Navneet Kaur *et al., 2011* indicated that most numbers of cases were observed in 35 to 44 years of age. Another study by Ramchandra Kamath *et al., 2013* had observed that the mean age of the patients was 45.64 years. Our study had similar findings and the mean age of the patients was 48.88 years. This indicates that with an increase in age, the chances of breast cancer increases. Most of the patients were in a post-menopausal state. Several changes occur in a post-menopause state such as hormonal imbalance, disturbed metabolism, etc. that enhance the chances of breast cancer.

Present study was conducted to investigate the effectivity of the LDH, lipase, and ALP as a diagnostic marker for early diagnosis of breast cancer. In our study, the mean LDH level in the patients was 616.87±454.16 U/L. It correlates with several other studies such as by Vijay Shrivastava *et al.,* 2016 found that the mean level LDH in patients was 673.10±221.35 U/L. Our findings correlate with the study of Chandrakanth *et al.,* 2011 who found the mean serum LDH levels are significantly elevated in breast cancer than in fibroadenoma cases. Similar findings were also observed by Abdalla M Jarari *et al.,* 2011, Sandhya Mishra *et al.,* 2004 and Anupama Shrinivasan *et al.* 1999. They found a significant elevation in serum levels of LDH in breast cancer patients as compared to controls. A study performed by Amritpal Kaur *et al.,* 2015, Chandrakanth *et al.,* 2011, Anupama Shrinivasan *et al.,* 1999 and Seth L R *et al.,* 2003 they found that serum LDH levels increased significantly with increasing severity of carcinoma breast (from stage I to stage IV). In our study serum levels of LDH were higher in breast cancer patients. This enzyme might therefore be a supportive biochemical marker along with clinical and histopathological findings for predicting breast cancer metastasis.

The mean lipase level in the patients was found to be 65.81±51.69 U/L and 31.81% of patients had higher lipase value in our study. The results of our study correlate with the study of Meizi Cui *et al.,* 2014 who had found a higher expression level of lipase in breast cancer patients. In their study, 64.74 % (224/346) had a high expression of lipase. In our study serum levels of lipase were higher in breast cancer patients suggesting an immense potential of lipase as an additional biomarker for the prediction of breast cancer metastasis early.

The mean ALP level was found to be 55.76±17.42 U/L in the breast cancer patient. No significant increase was seen in the patients. Similar to this study Von Hoof *et al.,* 2000 and Sandhya Mishra *et al.,* 2004 also did not find any significant difference in ALP levels in non-metastatic breast cancer. Ying Jin *et al.,* 2015 had done a similar study on a large scale and they found that 50% of breast cancer patients with metastasis had higher expression levels of serum ALP. Vijay Shrivastava *et al.,* 2016 had done a similar kind of study and found that the serum levels of ALP were significantly higher in breast cancer patients. The mean values of serum ALP were 98.3 ±51.4 U/L. Amritpal Kaur *et al.,* 2015 and Choudhari *et al.,* 2013 had found that the levels of serum ALP were significantly higher in patients of carcinoma breast as compared to controls. Study conducted by ali et al., 2018 in Iraqi women showed that there is an significant increase in serum LDH, ALP and lipid profile in breast cancer patients as compared to control.

Based on the results found in our study and its correlation with other studies it can be concluded that to establish the prognostic value of ALP in the prediction of metastasis in breast cancer patients there is a need for a large-scale study as the results are not significant.

CONCLUSION

The benefits of evaluating the effectiveness of these parameters are that they are simple, fast, and comparatively cheaper and can be easily performed with smaller labs with no need of advanced equipment. In a large retrospective study, if promising findings are obtained with the correlation of the clinical history and in-depth follow-up of patients, it will offer a new and affordable way to identify patients at a greater risk of metastatic breast cancer, increasing the expectation that screening can be focused, resulting in early diagnosis of disease progression and thus lower the morbidity and mortality of the disease.

The main limitation of the research is that it is observational, confined to a particular area, and the sample size was quite small to support the effect of various clinical characteristics and enzyme levels on survival. Thus it was not possible to generalize the obtained findings to other populations. The diagnostic importance of the levels of these biomarkers should be evaluated in a large prospective design for verification and to recognize the systemic inflammatory process and its function in altering the microenvironment of tumors.

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CONFLICT OF INTEREST:

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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