Research Article

Study of Serum Lactate Dehydrogenase, Alkaline Phosphatase and β - hCG in Women with Palpable Breast Lesions – A Cross-Sectional Study

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ABSTRACT

BACKGROUND: Globally, breast cancer ranks 2nd in cancer incidence. Both benign lesions and cancers present as lumps. Early detection of cancer is vital for treatment; there is need for a simple, sensitive method to detect tumours early.

OBJECTIVES: This study aimed to assess diagnostic value of serum Lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and β-human chorionic gonadotropin (β-hCG) levels in women with palpable breast lesions.

METHODS: This cross-sectional study, spanning 2 years, included 192 women (18 – 80 years) coming to Department of Surgery, JNIMS, presenting with breast lumps. LDH was measured by DGKC method, ALP and β-hCG were measured by ELISA. Descriptive statistics, independent samples t-test and chi-square test were used for biomarker changes in benign and malignant lesions, receiver operating characteristic (ROC) curves for diagnostic performance.

RESULTS: 129(67.2%) of patients had benign lesions and 63(32.8%) had malignant lesions. Mean LDH was significantly lower in benign cases (294.9 ± 78.21 U/L) than malignant cases (448.2 ±168.0 U/L) (p-value < 0.05). Mean ALP was significantly lower in benign cases (619.86 ± 284.01 pg/ml) than malignant cases (817.47 ± 334.34 pg/ml) (p-value < 0.05). β-hCG was significantly raised in 17(8.8%) of malignant cases and undetectable in benign cases (n=129,67.2%) and 46(24%) of malignant cases (p-value < 0.05). β-hCG showed superior performance (AUC=0.839), followed by LDH (AUC= 0.773) and ALP (AUC=0.685).

CONCLUSION: β-hCG exhibited the best discriminatory ability, followed by LDH, while ALP performed poorest. The findings suggest their potential role in improving diagnostic accuracy. Validation through large scale studies is warranted.

Keywords: *Breast cancer, Lactate Dehydrogenase (LDH), Alkaline Phosphatase (ALP), β-Human chorionic gonadotropin (β-hCG), Diagnostic performance*

1. INTRODUCTION

Breast cancer has become the second leading cause of global cancer incidence in 2022 representing 11.7% of all cancers. As per the Globocan data 2022, India ranks third with 192,020 new cases of breast cancer and ASR of 26.6 %. India has the highest number of deaths due to breast cancer in 2022 with ASR of 13.7% as compared to the global ASR of 12.7% [1].

Risk of developing breast cancer is multifactorial which may be, genetic, environmental and histological factors. Risk is increased in women with a family history of breast cancer, hormone replacement therapy, high fat diet, obesity, radiation exposure and alcohol consumption [2]. Female reproductive history also highly influences breast cancer. Early menarche, nulliparity, short lactation period and late menopause increase the duration of ovarian hormone exposure and increases the risk, while bilateral oophorectomy reduces risk of breast cancer.

Clinically, the most common symptoms of breast cancer include the presence of a lump, nipple discharge, change in the size or shape of breasts. These are similar to those of benign conditions like fibroadenoma of the breast; limiting the clinical differentiation between benign conditions and carcinoma breast [3]. The rich vascular and lymphatic supply of breast, facilitates the spread of tumour-derived substances into the systemic circulation [4]. These anatomical features consequently give rise to the spectrum of various diseases and the associated derangement of biochemical analytes detectable in serum.

Cancer cells replicate rapidly so the enzymes and proteins in the nucleus, cytoplasm and mitochondria are released into circulation at enhanced rate and can be measured and analyzed. The most relevant biomarkers associated with breast cancer include genetic markers like Breast Cancer Type (*BRCA1*, *BRCA2*), and protein biomarkers like hormone receptors (estrogen and progesterone receptors), cancer antigen CA 27.29, carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2). Of date, no ideal marker has been proven to be a sensitive and specific indicator of early breast cancers [5].

Therefore, there is a need for a simple, noninvasive and sensitive method to detect and differentiate tumors early, when they are small in size. This study was taken up to assess the diagnostic value of serum LDH, ALP and β-hCG levels in women with palpable breast lesions.

In cancer, the gene for LDH-A protein is often upregulated in tumours and is required for their maintenance and progression [6, 7]. Increased cellular turnover and metabolic activity in breast lesions may lead to altered LDH levels, reflecting tissue damage and enhanced glycolytic metabolism (Warburg Effect) [8, 9].

Alkaline phosphatase levels may also be influenced by tissue remodeling and ectopic enzyme expression associated with proliferative breast lesions [9, 10, 11].

Several studies have evaluated these enzymes collectively to assess disease activity and progression in breast lumps. Variations in serum LDH and ALP levels have been reported in both benign and malignant breast conditions, demonstrating their potential utility as biomarkers. Expression of oncofetal proteins such as β-hCG has also been reported in certain breast lesions, highlighting a possible role in tumor biology and disease behaviour [12, 13].

2. MATERIALS AND METHODS

The present study was a hospital based cross-sectional study conducted in the Department of Biochemistry in collaboration with the Department of Surgery, Jawaharlal Institute of Medical Sciences, Porompat, Manipur, after obtaining approval from the Institutional Ethics Committee, JNIMS. The study was carried out over 2 years (April 2024 - March 2026). Based on the prevalence of breast lumps (46%) and taking confidence interval 95% and allowable error at 7%, sample size was calculated to be 192 using the formula:

Sample size(n)=$Z^2P(1-P)/d^2$

Informed written consent was obtained from all participants prior to inclusion.

Inclusion criteria:

In-patients and out-patients of the Department of Surgery, JNIMS, Imphal in age group 18 – 80 years, presenting with palpable breast lesions which were newly diagnosed as benign or malignant cytologically or histo-pathologically.

Exclusion criteria:

- Patients who did not give consent
- Patients with:
  - Myocardial infarction
  - Liver, kidney and pancreatic diseases
  - History of alcoholism
  - Hematologic disorders
  - Bone diseases
  - Diabetes mellitus
  - Patients taking antiepileptic drugs or hepatotoxic drugs
  - Current pregnancy
  - Gestational trophoblastic disease.
  - Other malignancies.

A predesigned proforma was used to record detailed history and clinical findings.

After taking informed consent,5 ml of venous blood was drawn under aseptic conditions from all participants. Samples were allowed to clot and serum separated by centrifugation. The serum

was aliquoted and analyzed immediately or stored 2-8^{0}C for up to 48 hours and for longer periods at -20^{0}C.

Serum LDH was measured using DGKC method with the help of Meril Merilyzer CliniQuant Micro. Serum ALP and serum β-hCG were estimated by Sandwich-ELISA using Alere Easy Reader. Serum LDH values >460 U/L was considered elevated. Values above the 97.5th percentile of ALP values of patients with benign lesions were considered elevated. For β-hCG, a commercial ELISA kit with a lower limit of detection (LLoD) of 7.81 mIU/mL was used. Values below the detection limit were reported as < LLoD (undetectable) and were assigned a value equal to half of the detection limit for analysis.

STATISTICAL ANALYSIS

Statistical analyses were carried out using the SPSS software package, version 27. Two-sided $p<0.05$ was considered as level of significance. Descriptive statistics like mean, median, standard deviation (SD) and analytical statistics like independent samples t- test and Chi-square test were used.

3. RESULTS

The present study was carried out at Jawaharlal Nehru Institute of Medical Sciences, Imphal from February 2024 to March 2026. A total of 192 women presenting with palpable breast lesions were included in the study. The lesions were divided into benign and malignant.

Table 1: Mean age of patients with benign and malignant lesions. (n=192)

LESION TYPE	MEAN AGE (Years)	p-value
BENIGN LESIONS	30.4 ± 10.5	<0.05
MALIGNANT LESIONS	57.1 ± 11.4	

The mean values of Age ± SD of the patients with benign lesions is 30.4 ± 10.5 years and of patients with malignant lesions is 57.1 ± 11.4 years respectively with a significant value<0.05.

The benign lesions accounted for 129 cases (67.2%) while 63 (32.8%) of the cases were malignant. Fibroadenoma was the commonest benign lesion with 91 cases (47.3%), followed by fibrocystic disease accounting for 16 of the cases (8.3%). The majority of malignant cases was comprised of invasive ductal carcinoma with 66 cases (34%).

Table 2: Distribution of breast lesions according to type. (n=192)

Lesion types	Benign lesions n (%)	Malignant lesions n (%)	Total n (%)
Breast cyst	3(1.6%)	-	3(1.6%)
Ductal hyperplasia	9(4.7%)	-	9(4.7%)
Fibroadenoma	91(47.3%)	-	91(47.3%)
Fibrocystic disease	17(8.8%)	-	17(8.8%)
Papilloma	2(1.0%)	-	2(1.0%)
Phyllodes' tumour	2(1.0%)	-	2(1.0%)
Antibioma (ANB)	1(0.5%)	-	1(0.5%)
Invasive ductal carcinoma	-	62(32.3%)	62(32.3%)
Lobular carcinoma	-	1(0.5%)	1(0.5%)
Total	129 (67.2%)	63(32.8%)	192

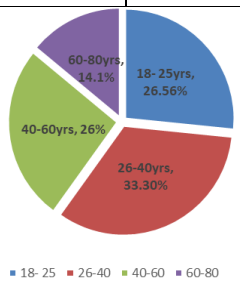


Figure 1: Pie chart showing overall distribution of breast lumps with age.

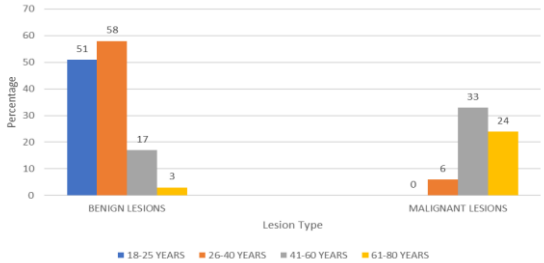


Figure 2: Clustered column diagram showing age wise distribution of the cases in percentage.

As depicted in figure 1 & 2, 4 1 - 60 years age group showed the maximum number of malignant breast lesions constituting 17.2%(n=33) and 26 – 40 years age group constituting 3.1%(n=6) had the least. The highest number of benign lesions was seen in 26 – 40 years age group constituting 30.2%(n=58). Overall, the most breast lumps were seen in the reproductive age group. (Fig 1)

Table 3: Distribution of cases according to parity (n=192).

PARITY	BENIGN LESIONS	MALIGNANT LESIONS	p-value
Nulliparous	82 (42.7%)	3 (1.5%)	
Parous	47 (24.5%)	60 (31.3%)	< 0.05
Total	129 (67.2%)	63 (32.8%)	

Majority of the benign cases were nulliparous accounting for 42.7% of the cases (n=82) while the 60 (31.3%) cases out of 63 malignant cases were parous showing a significant difference (p-value<0.05).

Table 4: Mean LDH and mean ALP values in benign and malignant cases. (n=192)

	Benign lesions	Malignant lesions	p-value
Mean Serum LDH (U/L)	294.9 ± 78.21	448.2 ± 168.04	<0.05
Mean Serum ALP (pg/ml)	619.86 ± 284.01	817.47 ± 334.34	<0.05

Both the mean serum LDH and ALP levels were significantly higher in malignant cases as compared to benign cases with a p-value <0.05.

Table 5: Distribution of cases according to serum LDH levels. (n=192)

	Normal (230–460 U/L)	Elevated (>460 U/L)	TOTAL	p-value
Benign Lesions	103(53.6%)	26(13.5%)	129(67.2%)	
Malignant Lesions	11(5.75%)	52(27.1%)	63(32.8%)	
Total	114(59.3%)	78(40.65)	192	<0.05

103(53.6%) out of 129 benign cases had normal serum LDH levels while 52(27.1%) out of 63 malignant cases had elevated serum LDH levels with a statistically significant difference ($p < 0.05$), indicating a significant association between type of lesion and serum level of LDH.

Table 6: Distribution of cases according to serum ALP levels. (n=192)

Serum ALP Levels	Malignant Lesions	Benign Lesions	Total	p-value
ELEVATED (> 97.5th Percentile)	10(5.2%)	4(2%)	14(7.3%)	<0.05
WITHIN RANGE (≤ 97.5th Percentile)	53(27.6%)	125(65.1%)	178(92.7%)	
Total	63(32.8%)	129(67.2%)	192(100%)	

Elevated levels were observed in 10(5.2%) of the malignant cases as compared to 4(2%) of the benign cases. Majority of benign as well as malignant cases had ALP levels within the study-derived reference range. There was a statistically significant association between ALP elevation and type of lesion($p<0.05$).

Table 7: Distribution of cases according to serum β-hCG levels. (n=192)

Serum β-hCG	Benign Lesions	Malignant Lesions	p-value
Undetectable	**129(67.2%)**	**46(24%)**	
(<7.81mIu/ml)			**<0.05**
Raised	**0**	**17(8.8%)**	

All of the benign cases had undetectable serum β-hCG levels as compared to 46(24%) of the malignant cases having undetectable levels and 17(8.8%) showing raised serum levels with a statistically significant difference ($p <0.05$).

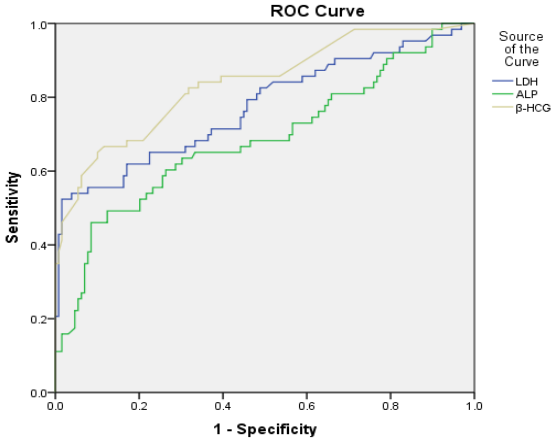


Figure 3: Comparative diagnostic performance of LDH, ALP and β-hCG.

β-hCG was the most reliable serum marker for distinguishing malignant from benign breast lesions (AUC of 0.839). LDH showed moderate discriminatory power, reflecting its association with increased cellular turnover and tissue damage in malignancy (AUC of 0.773). ALP demonstrated limited diagnostic value as an independent marker (AUC of 0.685). These findings support the role of β-hCG and LDH as useful adjunctive serum markers in the evaluation of palpable breast lesions.

Table 8: Diagnostic performance and optimal cut-off values of evaluated biomarkers.

Biomarker	AUC (95 % CI)	Diagnostic Accuracy	Optimal Cut-off	Sensitivity (%)	Specificity (%)
LDH	0.773	Good	~240 U/L	74%	72%
ALP	0.685	Fair	~300 pg/ml	68%	65%
β-hCG	0.839	Very Good	≥7.81 mIU/ml	27%	100%

At the optimal cut-off value, β-hCG exhibited a sensitivity of approximately 27% and specificity of 100%, indicating superior discriminative ability compared to LDH (sensitivity= 74%, specificity=72%) and ALP (sensitivity=68%, specificity=65%). All three markers were statistically significant ($p < 0.05$).

4. DISCUSSION

Breast cancer continues to be a major public health issue, being the most frequently diagnosed malignancy in India and second most incident malignancy globally. Disease progression and severity is dependent on many factors, including genetic predisposition, environmental factors, hormone receptor expression and histological grade. Since the morbidity and mortality as well as treatment costs increase with advanced disease, early diagnosis can help lower the burden on patients. Several studies have been conducted to evaluate the role of biochemical markers in the diagnosis of breast malignancy. In light of this, the present study was conducted on 192 patients presenting with palpable breast lesions.

Benign lesions accounted for the majority of the cases (67.2%) while malignant lesions accounted for 32.8%. Fibroadenoma was the commonest type of lesion among the benign lesions (47.3%). The predominance of fibroadenoma in younger age group may be attributed to hormonal influences as well as high incidence in reproductive age group. This finding is in line with the studies of Malherbe *et al.*, [14] and Johansson *et al.,* [15]. Invasive ductal carcinoma represented the predominant malignant lesion (32.3%). This observation conforms to global epidemiological data [1].

The mean age of patients with benign cases was 30.4 ± 10.5 years whereas malignant cases had a significantly higher mean age of 57.1 ± 11.4 years (p-value<0.05). Malignant lesions predominated in patients above 40 years of age. The highest proportion of malignancy was noted in the 41- 60 years age group (17.2%), followed by 61-80 years (12.5%). Conspicuously, no malignant cases were observed in the 18 - 25 years age group. The association between type of lesion and age was statistically significant($p<0.05$), highlighting advancing age as an important risk factor for breast malignancy. These findings may be attributed to hormonal influences and age-related genetic factors which increases susceptibility to malignancy over time. The increased incidence of malignant lesions in older age group reflects the effects of cumulative hormone exposure, genetic predisposition and environmental factors. The findings were in conjunction with previous literature; notably, of Malherbe *et al.,* [14] and Ahmad [16].

This study also demonstrated a statistically significant association between parity and type of lesion($p<0.05$). Malignant lesions were more commonly observed among parous women (31.3%) compared to nulliparous women (1.5%), while benign lesions were more frequent in nulliparous women (42.7%). This finding is in contrast to the widely accepted fact that nulliparity is a risk factor to malignancy.

Young age at first childbirth is considered to be protective against breast cancer. However, the higher proportion of malignancy in parous women in this study may be attributed to the higher number of older women in the parous age group. Age may act as a confounding variable in this association, which could be prevented by use of multivariate analysis to determine whether parity is an independent risk factor for malignancy.

In this study, all of the benign cases had undetectable serum β-hCG levels while 46(24%) of the malignant cases had undetectable levels and 17(8.8%) showed raised serum levels ($p<0.05$). In ROC curve analysis, β-hCG exhibited a sensitivity of 27% and specificity of 100% with AUC=0.839, showing superior diagnostic performance. Elevated β-hCG levels in malignant cases could be due to ectopic production by cancer cells and its role in cellular proliferation, angiogenesis and immune modulation. These findings were in concordance with the findings of Mohammed *et al.,* [17] and Monteiro *et al.,* [18] where malignant cases had statistically higher hCG levels than the benign cases. Al-Rawi *et al.,* [19] observed that β-hCG was expressed in 6 out of 36 malignant breast tumors; in contrast to benign breast lesions, none of which showed β-hCG expression. The findings of the present study align with theirs.

It is pertinent to note that the ELISA kit used in this study had a relatively higher lower limit of detection (LLoD), which may have influenced the clustering of the benign values near the detection limit. Despite this, β-hCG retained significant discriminatory ability, promotes its robustness as a diagnostic marker.

The mean serum LDH levels were significantly higher in malignant cases (448.2 ± 168.04 U/L) than in benign cases (294.9 ± 78.21 U/L) ($p<0.05$). This elevation may indicate tumour burden and cellular turnover associated with malignancy. Considering the ROC analysis, LDH showed fair to good performance compared to β-hCG, with an AUC of 0.773, sensitivity of 74% and specificity of 72%. The elevation of LDH in malignancy may be explained by increased anaerobic glycolysis (Warburg effect). Malignant cells rely on anaerobic glycolysis, leading to increased lactate production and elevated LDH activity. Thus, serum LDH may reflect tumor metabolic activity. Similar findings were observed by Agarwal *et al.,* [20] and Radenkovic *et al.,* [21] where LDH levels were found to be higher in patients with breast malignancy and also corresponded with clinical stage and bulk of the tumor. Mehta *et al.,* [22] also found in their study, higher expression of LDH in 50% of breast cancer patients. This finding aligns with those of the present study.

Despite its elevation in malignancy, overlapping LDH values between benign and malignant cases may reduce its specificity. This may be due to tissue injury, inflammatory changes or benign proliferative conditions as LDH can be mildly elevated in these conditions. Overall, LDH may have more utility as a supportive biomarker rather than a standalone diagnostic marker. The prognostic relevance of LDH needs assessment, particularly in advanced disease and metastatic malignancy.

In the present study, the mean serum ALP level was significantly higher in malignant cases (817.47 ± 334.34 pg/ml) than in benign (619.86 ± 284.01 pg/ml) ($p<0.05$). 10 out of 63 malignant cases had elevated ALP levels while, majority of the benign cases had ALP levels within the study derived reference range. Despite the statistically significant difference between mean levels between benign and malignant cases, ROC analysis revealed that ALP had comparatively lower discriminatory ability between benign and malignant lesions with an AUC of 0.685, sensitivity of 68% and specificity of 65%. Substantial overlap in the ALP values between benign cases and malignant cases existed even though a mild elevation was seen in certain malignant cases.

Similar findings were observed by Shrivastava et al.[23], Choudhari et al.[24] and Chandrakanth et al.[25] where the ALP levels were significantly higher in malignant lesions than fibroadenoma cases. Elevated levels of ALP in malignant cases may be due to metastasis to bone and/or liver, or tumor induced tissue remodeling. However, in early stages of malignancy, ALP elevation may be minimal. This can explain the mild elevation observed in the present study. A study conducted by Fushimi et al., [13] on human breast cancer MDA-MB-231 cell line demonstrated microcalcifications occurring when cultured in an osteogenic cocktail-containing medium. This finding reveals that breast cancer cells acquire ALP enzyme activity which indicate possible ectopic production by the cancer cells. This may potentially explain the elevation seen in some of the malignant cases in the present study.

While ALP can reflect certain changes associated with malignancy, its role seems to be rather supportive than definitive in differentiating malignant from benign lesions. ALP may have more relevance as a prognostic marker than diagnostic biomarker. Variability of ALP performance across studies may be influenced by population selection, analytical methods and the disease stage.

Collectively, the findings of the present study suggest an association between the biochemical parameters studied and the histopathological nature of palpable breast lesions. Serum LDH and ALP levels were significantly higher in malignant lesions compared with benign lesions, which may be attributed to increased cellular turnover, altered metabolism and remodelling associated with malignancy. Serum β-hCG was observed predominantly among malignant lesions and was not detected in any of the benign lesions, demonstrating a particularly strong association with malignancy. The ROC curve analysis further demonstrated the ability of these parameters to discriminate between benign and malignant breast lesions, with β-hCG showing the highest diagnostic performance, followed by LDH and ALP. These findings suggest that the studied biochemical parameters may reflect

biochemical alterations associated with malignant nature of palpable breast lesions. However, their limited specificity and the overlap in values between benign and malignant lesions limit their utility as substitutes for clinical, radiological and histopathological evaluation and instead, may have potential as adjunctive markers.

The present study had certain limitations. Being a single-center study in a tertiary care hospital, the findings are not generalizable to other settings. Selection of participants were limited to those whose medical information could be retrieved from the medical records. The relatively higher lower limit of detection of the ELISA kit may have resulted in clustering of low β-hCG values among the benign cases. Additionally, multivariate adjustment for potential confounders like age and parity was not performed.

5. CONCLUSION

The present study demonstrates that β-hCG possess the highest diagnostic potential in differentiating benign and malignant lesions followed by LDH while ALP had the poorest performance. The degree of discriminatory ability differs between the three biomarkers even though statistically significant differences were observed between the groups. Advancing age was strongly associated with malignancy, solidifying its role as an important risk factor in malignancy. Age related confounding factors influenced the association of lesion type with parity. Overall, β-hCG appears to be a promising biomarker in the evaluation and differentiation of breast lesions. Currently, these serum biomarkers can be considered as adjunctive tools to support clinical and radiological examination. Their potential use as prognostic tools needs further assessment.

However, if these findings could be replicated in large-scale, multicentric studies with larger sample size using multivariate analysis and combined biomarker assessment, the findings could be validated and their potential utility in routine clinical practice could be established. These biomarkers could potentially become an affordable, accessible and reliable means to screen early breast malignancy.

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CONFLICTS OF INTEREST

None declared.

ETHICAL CONSIDERATION

Approved by the institutional ethics committee as per notice no.Ac/03/IEC/JNIMS/2018-PGT

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