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Serum Prolactin: A Clue to Breast Malignancy

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ABSTRACT

Background and objectives: Prolactin is a lactogenic protein hormone secreted by the anterior pituitary that initiates and maintains lactation in mammals. Previous research has linked increased serum prolactin levels to breast cancer. However, there is a paucity of studies in the Indian population on the subject. The present study evaluated and compared serum prolactin levels in patients with breast cancer and patients with benign breast diseases.

Methods: This cross-sectional, comparative study was carried out at the Government Medical College, Nagpur (India) on patients with breast diseases in the out-patient department/in-patient department from June 2018 to November 2020. Breast cancer patients were considered cases, and those with benign breast diseases were considered controls. Breast carcinoma diagnosis was based on clinical features, fine needle aspiration cytology, and tissue histopathology in operated specimens for each patient. Fasting serum prolactin levels were measured by the chemiluminescence immunoassay method using the Advia Centaur immunoassay system.

Results: There were 120 female patients with breast diseases, of whom 60 had breast malignancy, and 60 had benign breast diseases. The mean age of patients with benign breast disease and breast cancer was 33.17 (1.75) and 49.77 (1.16) years, respectively ($P<0.0005$). Increased serum prolactin levels were observed in 93.3% of patients with breast cancer and 13.3% of patients with benign breast diseases. The mean serum prolactin level was significantly higher among breast cancer patients (102.68±7.03) ng/ml compared with patients with benign breast disease (16.31±1.72 ng/ml). We successfully determined a new cut-off value of serum prolactin level (>40.2 ng/ml) to differentiate breast cancer from benign breast diseases using the receiver operating characteristic curve analysis.

Conclusion: Patients with breast cancer have increased serum prolactin levels compared to patients with benign breast diseases. Thus, serum prolactin level can be used as a diagnostic marker for breast cancer. This is particularly beneficial to clinicians for differentiating breast cancer from benign breast diseases.

Keywords: Prolactin, Biomarkers Tumor, Breast Neoplasms.

INTRODUCTION

Breast cancer is one of the most prevalent malignancies in women. According to the Global Cancer Observatory (GLOBOCAN) 2020 estimates, the incidence of breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases globally (1). Breast cancer is also the leading malignancy among Indian women, with an age-adjusted rate of 25.8 per 1,00,000 females and a mortality rate of 12.7 per 1,00,000 females (2). Breast cancer estimates for India during 2020 indicate a rise to 17,97,900 (3).

Prolactin is a well-defined lactogenic protein hormone secreted by the anterior pituitary that initiates and maintains lactation in mammals (4). It facilitates the dissemination of epithelial breast cells and alveoli differentiation. Several risk factors for breast cancer, such as nulliparity and elevated mammographic breast density, have been associated with high serum prolactin levels. Many laboratory studies have shown that prolactin can cause cell proliferation, tumor vascularization, and cell motility, which work independently and synergistically to facilitate late-stage breast cancer carcinogenesis and increase its potential to metastasize to distant organs (5). Increased prolactin levels in the blood have been linked to breast cancer (5–7); however, there is a paucity of studies in the Indian population on the subject. The present study evaluated serum prolactin levels in patients with breast cancer and benign breast diseases in an Indian population.

MATERIALS AND METHODS

This cross-sectional, comparative study was carried out at the Government Medical College, Nagpur (India) on patients with breast diseases in the out-patient department/in-patient department from June 2018 to November 2020. The Institutional Ethics Committee approved the study, and written consent was obtained from all patients prior to their enrollment in the study. Breast carcinoma patients were considered cases, and those with benign breast diseases served as control. Breast carcinoma diagnosis was based on clinical features, fine needle aspiration cytology, and tissue histopathology in operated specimens for each patient. Inclusion criteria were confirmed diagnosis of malignant/benign breast diseases, 18 years and above age, and willingness to participate in the study. Male patients, pregnant/lactating women, and patients currently receiving phenothiazines, L-Dopa, monoamine oxidase inhibitors, or other drugs known to affect prolactin's secretion were excluded from the study. With a power (1-β) of 80% and an alpha error of 5%, the calculated sample size was 120, including 60 cases with breast malignancy and 60 controls with benign breast diseases. Overall, 120 patients were selected using a total enumerative sampling technique.

Specimen collection and preservation

Fasting blood samples (2 ml venous blood) were collected to estimate serum prolactin levels. All samples were collected between 8 am and 9 am. Anticoagulants were not used for blood collection. The serum was promptly separated, and the test was done on the same day. Prolactin is stable in serum for three weeks when stored at 2-8°C and for seven days when stored at 15-25 °C.

Estimation of serum prolactin level

Serum prolactin levels were measured by the chemiluminescence immunoassay method using a commercial kit (Siemens ADVIA Centaur® Prolactin Test Kit) and the Siemens Advia Centaur Xpt Immunoassay fully automated analyzer. Reference intervals of serum prolactin (As per equipment's set reference standard) were as follows: Adult non-pregnant female: 3-29 ng/ml, pregnant female: 10-209 ng/ml, and adult males: 3-13 ng/ml. Chemiluminescence immunoassay is an assay that combines the chemiluminescence technique with immunochemical reactions. In the presence of complementary antigen and antibody, the antibody's paratope binds to the antigen's epitope to form an antigen-antibody or an immune complex. Levels of this immune complex using labelled antibodies are estimated. The substrate is added post-incubation, which ensures that intact immune complexes are formed. This results in the generation of light, the intensity of which is directly proportional to the amount of labelled complexes present. The intensity of light is measured in terms of relative light units.

Statistical analysis

Quantitative data were expressed as the mean and standard error of the mean (SEM). Categorical data were summarized as frequencies and proportions. The prolactin level among breast cancer patients and women

with benign breast diseases was compared using the t-test and chi-square test. An arbitrary cut-off of 0.05 was considered to indicate the significance of the p-value.

Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of serum prolactin level to differentiate breast malignancy from benign breast diseases. The area under the ROC curve (AUC) results were considered excellent for AUC values between 0.9-1, good for AUC values between 0.8-0.9, fair for AUC values between 0.7-0.8, poor for AUC values between 0.6-0.7, and failed for AUC values between 0.5-0.6. Different cut-off points for serum prolactin levels were tested to categorize the data as benign or malignant. The optimum cut-off point was defined as that which maximized the AUC value. The Youden index J was utilized for determining the optimum cut-off value of serum prolactin level for differentiating breast malignancy from benign breast disease.

RESULTS

The mean age of patients with benign breast disease and breast cancer was 33.17 (1.75) and 49.77 (1.16) years, respectively (P<0.0005). Increased serum prolactin levels were observed in 93.3% of patients with breast cancer and 13.3% of patients with benign breast diseases. The mean serum prolactin level was significantly higher among breast cancer patients (102.68±7.03 ng/ml) compared with patients with benign breast disease (16.31±1.72 ng/ml). The increased serum prolactin levels in patients with breast malignancy compared to patients with benign breast disease was observed across all ages (Figure 1).

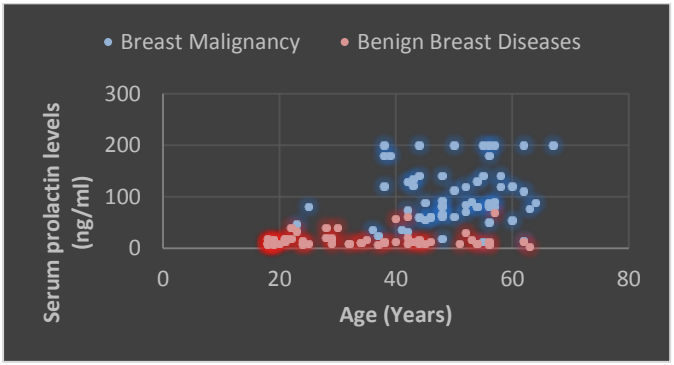

Figure 1- Distribution of serum prolactin levels in patients with breast malignancy and benign breast diseases with age.

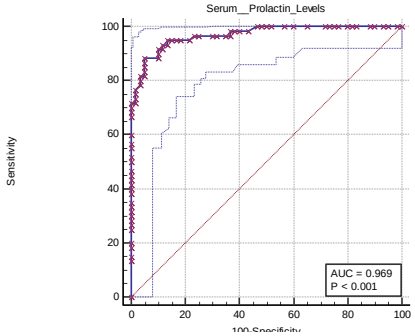

Figure 2- The ROC curve of serum prolactin. Perfect discrimination has a ROC plot passing through the upper left corner (100% sensitivity, 100% specificity). The closer the ROC plot to the upper left corner, the higher the test's overall accuracy (AUC: 0.9-1 indicating excellent; 0.8-0.9 indicating very good; 0.7-0.8 indicating good; 0.6-0.7 indicating average; 0.5-0.6 indicating poor). The AUC of serum prolactin was 0.969.

Receiver operating characteristic (ROC) curve analysis

As shown in figure 2, the ROC analysis showed that the AUC was 0.969 (95% CI: 0.921 to 0.992) (Figure 2). The detailed parameters of the ROC curve analysis are shown in table 1. As per the Youden index J (0.8333), the optimum cut-off value of serum prolactin that demonstrated the maximum sensitivity (88.33%) and specificity (95%) for differentiating breast malignancy from benign breast disease was 40.2 ng/ml.

Table 1-The detailed parameters of the ROC curve analysis

The area under the ROC curve (AUC)	**0.969**
Standard error [a]	**0.0128**
95% confidence interval	**0.921 to 0.992**
z statistic	**36.621**
Significance level P (Area=0.5)	**<0.0001**
Cut off value analysis of serum prolactin level	
Youden index J	**0.8333**
Associated criterion (of serum prolactin level)	**>40.2 ng/ml**
Sensitivity	**88.33%**
Specificity	**95.00%**

[a] DeLong et al., 1988

This cut-off value showed higher diagnostic accuracy for breast cancer than the 29 ng/ml conventional standard value (91.67% vs. 90%).

The detailed Comparative parameters of the new cut-off value of serum prolactin level (40.2 ng/mL) vis-à-vis the standard cut-off value (29 ng/ml) are described in table 2.

Table 2- Comparative test parameters of serum prolactin levels for diagnosing breast malignancy at the new cut-off value (>40.2 ng/ml) and the standard cut-off value (>29 ng/ml)

Test parameters of serum prolactin levels for diagnosing breast malignancy	At serum prolactin cut off value of >40.2 ng/ml			At serum prolactin cut off value of >29 ng/ml		
	Value	95% CI		Value	95% CI	
Sensitivity	88.333%	77.428%	95.179%	93.333%	83.801%	98.154%
Specificity	95.000%	86.076%	98.957%	86.667%	75.408%	94.064%
Accuracy	91.667%	85.208%	95.931%	90.000%	83.183%	94.725%
Positive predictive value	94.643%	85.382%	98.163%	87.500%	78.537%	93.051%
Negative predictive value	89.062%	80.194%	94.245%	92.857%	83.383%	97.117%
Positive likelihood ratio	17.667	5.841	53.435	7.000	3.659	13.391
Negative likelihood ratio	0.123	0.061	0.247	0.077	0.030	0.199
Number needed to diagnose	1.2	1.105	1.450	1.25	1.13	1.54
Number needed to misdiagnose	12	6.445	21.037	10	5.704	17.411

CI: confidence interval.

DISCUSSION

We observed that a substantially larger proportion of breast cancer patients had raised serum prolactin levels than patients with benign breast diseases. In addition, breast cancer patients had a significantly higher mean serum prolactin level than patients with benign breast diseases. We further constructed the ROC curve and analyzed the diagnostic value of serum prolactin level in breast cancer. Using the ROC curve analysis, we successfully determined a new cut-off value of serum prolactin level (>40.2 ng/ml), which could help differentiate breast malignancy from benign breast diseases. Compared to the current standard cut-off value of serum prolactin level (>29 ng/ml), this new cut-off value demonstrated a greater diagnostic accuracy along with other improved parameters, including increased specificity, increased positive predictive value, increased positive likelihood ratio, decreased number needed to diagnose, and increased number needed to misdiagnose while balancing to an acceptable level, the parameters like sensitivity, negative predictive value, and negative likelihood ratio.

Many studies have been done on the potential link of prolactin with breast cancer development. Consistent with our findings, Walia et al. reported a significant increase in serum prolactin level in breast carcinoma patients compared with patients with benign breast disease (8). Similarly, another study indicated that the mean serum prolactin level in breast cancer patients (52.4 ng/ml) was significantly higher than in patients with benign breast disease (7.5 ng/ml) (9). A large-scale study by Tworoger et al. revealed similar findings on the potential relationship of prolactin with breast cancer (10). Reynolds et al. indicated that the expression of prolactin and the prolactin receptors (PRLR) occurs in many breast cancers at the RNA level when assessed by reverse transcriptase-polymerase

chain reaction (11). Jaffar et al. also reported a significant relationship between increased serum prolactin level and breast cancer (6). Another study also revealed that higher circulating prolactin is associated with an increased risk of *in situ* breast cancer (12). However, some studies have reported data that are inconsistent with our results. In one study, even though serum prolactin levels were higher in breast cancer patients than in controls, this elevation remained within the normal values (7). Dekkers et al. claimed that hyperprolactinemia is not linked to an increased risk of breast cancer since persistent hyperprolactinemia causes hypogonadism, which may lessen the risk of breast cancer by counteracting the tumorigenic impact of prolactin (13).

Prolactin, a pituitary hormone also released by mammary epithelia, is essential for mammary gland development, function, and lactation stimulation (14). This hormone may have a crucial role in breast cancer, according to substantial laboratory evidence (15). The precise mechanism through which high-normal circulating prolactin levels may lead to breast cancer is uncertain. Several critical events contribute to the malignant transformation of cells and the development of tumors, including cell proliferation stimulation and cell death inhibition (14). Prolactin protects human breast cancer cell lines against apoptosis, which could have crucial implications for cancer treatment (16). Hyperprolactinemia was almost always detected in individuals with metastatic breast cancer during the course of the disease, and it was a significant indicator of poor prognosis in node-positive breast cancer patients (17). Prolactin may boost the survival of breast cancer cells by inducing the production of new cancer cells and inhibiting cell death via the Janus-activated kinase-2/signal transducers and activators of transcription-5 (JAK2/STAT5) signaling pathway (18).

Prolactin-estrogen

crosstalk is bidirectional and can happen at var ious levels. Erα and Erβ transcription are increased by prolactin via STAT5. Prolactin can increase oestrogen sensitivity through this route, which has ramifications for tumor differentiation and therapy sensitivity. In several breast cancer cell lines, prolactin enhances epidermal growth factor-induced cell motility (19). Reuwer et al. found that prolactin is crucial for inducing angiogenesis due to direct interaction with endothelial cells, which was an important addition to our understanding of breast cancer progression (20). A few studies have found that breast tumors also express higher PRLR levels compared with adjacent healthy tissue (11). Recently, Sa-Nguanraksa et al. demonstrated a correlation between high PRLR expression and aggressive breast cancer (21).

Today, breast cancer is one of the leading malignancies globally, and research aiming at early diagnosis of this malignancy is essential to improve treatment outcomes. This study demonstrated that serum prolactin may be readily used as a marker for early breast cancer diagnosis. We proposed a new cut-off value (40.2 ng/ml) with improved diagnostic accuracy, different from the current standard cut-off value (29 ng/ml) of serum prolactin level for differentiating breast malignancy from benign breast diseases.

The procedural limitations of the present study are related to the immunoassay method utilized for serum prolactin estimation. As with any immunometric assay, prolactin is also susceptible to the high-dose hook effect, which may cause underestimation of prolactin (22). Gel filtration chromatography has been introduced as the gold standard method for quantifying isoforms of serum prolactin. However, it is time-consuming, expensive, and labor-intensive (23). Precise laboratory procedures for demonstrating hyperprolactinemia considering their potential utility in diagnosis and management of breast cancer are important. However, comparing the measured values across different prolactin measurement systems is difficult. The methodologies used in different laboratories vary, as do the reference ranges. This is one of the most challenging problems laboratories face when measuring prolactin (24). In addition to monomeric 23 kDa prolactin, two other distinctive forms are present in the circulation viz., ‘big prolactin’ and ‘big-big prolactin’ (macroprolactin). Big prolactin is the dimer of monomeric form, and big-big prolactin comprises high molecular mass (>150 kDa) complexes of 23 kDa prolactin and immunoglobulin G (IgG) autoantibodies. Both these forms have very little biological activity. Macroprolactin thus is mostly a prolactin complex with IgG, especially anti-prolactin autoantibodies. Anti-prolactin

autoantibodies attach to monomeric prolactin and produce a big prolactin-IgG immunological complex. Increased macroprolactin serum concentrations are a typical source of misdiagnosis, resulting in unnecessary and costly tests and therapies, as well as patient mismanagement. Currently, there is a considerable variability in routinely available prolactin immunoassays as a result of differing reactivity towards monomeric prolactin and macroprolactin and lack of commutability of the World Health Organization 3rd International Standard between routine methods. All routine assays detect macroprolactin to some extent, and laboratory practice in detecting and reporting macroprolactin has yet to be harmonized (22). Polyethylene glycol (PEG) precipitation is commonly used in laboratories to distinguish macroprolactinemia from true hyperprolactinemia. This approach is simple and affordable and has been thoroughly tested against GFC. Pre-treatment of sera with protein A, protein G, anti-human IgG, or ultrafiltration are all alternatives to PEG (25). The case and control groups were not age-matched in the present study, which can be a limitation of our study. Breast cancer is more common in older females as the risk increases with age, whereas benign breast diseases are typically seen in the younger age groups (26,27).

CONCLUSION

Patients with breast cancer have increased serum prolactin levels compared to patients with benign breast diseases. Thus, serum prolactin level can be used as a diagnostic marker for breast cancer. This is particularly beneficial to clinicians for differentiating breast cancer from benign breast diseases. It is recommended to conduct future studies with serum prolactin as a surrogate for therapeutic response to various treatment modalities in breast cancer.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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