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ORIGINAL ARTICLE

The Diagnostic Efficacy of Some Tumor Biomarkers for Breast Cancer Concerning Histopathological Examinations

Adel Nazum Radhi[1*], Mahdi Murshid Thwaini[1], and Hamed Jaddoa Abbas[2]

[1]College of Medical and Health Technology, Southern Technical University, Basrah 61004, Iraq
[2]Al-Fayhaa Teaching Hospital, College of Al- Zahraa Medical, Basrah University, Basrah 61004, Iraq

*Corresponding author:

adilalasadi86@gmail.com

College of Medical and Health Technology
Southern Technical University
Basrah, Iraq

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Abstract

Background Breast cancer (BC) remains the primary cause of mortality related to cancer. There is an increasing need for developing new and efficient diagnostic methods for early detection and diagnosis.
Purpose This study compared histopathological biopsies to tumor biomarkers (Serum P53, cathepsin D, cyclin E, and nestin) in diagnosing breast cancer.
Methods A case-control research included 60 breast cancer patients and 30 healthy controls. ELISA measured serum P53, cathepsin D, cyclin E, and nestin. The study found substantial increases ($P < 0.01$) in Nestin and Cyclin E levels in BC patients compared to the control group.
Results The study found a substantial drop ($P < 0.01$) in P53 levels in BC patients compared to the control group.The study found a substantial rise (P value < 0.01) in Nestin and cyclin E levels in BC patients with stage IV compared to early stages, but P53 decreased in increasing stages.There was a substantial positive connection ($P < 0.05$) between Cathepsin-D and cyclin E levels ($r= 0.210$). A strong negative connection ($P < 0.01$) exists between nestin levels and P53 levels ($r= -0.406$). The AUC analysis revealed sensitivity values of 0.33% and 0.43 for Nestin, P 53, Cathepsin-D, and Cyclin E markers, respectively. The study found sensitivity values of 0.62, 0.36, 0.40, 0.65, 0.20, and 0.33 for Nestin, P 53, Cathepsin-D, and Cyclin E markers.Breast cancer patients had higher Nestin and Cyclin E biomarkers and lower P53. Nestin and P53 have good breast cancer detection sensitivity and specificity.
Conclusion The study determined that nestin and P53 had a comparatively high level of sensitivity and specificity in the detection of breast cancer.

Keywords: Breast cancer; Tumor markers; P53; Cathepsin D, Cyclin E and Nestin

1 Introduction

Breast cancer is the most common type of tumor in women of all age groups, including those who are younger than 35 years old. It remains the primary cause of mortality related to cancer. Women below the age of 50 are not receiving screenings, leading to cancer diagnoses that depend only on clinical symptoms, a process that can be difficult and delayed [1].

Breast cancer is a global health concern, being the leading cause of mortality among women globally and also the most expensive disease to treat. As healthcare resources become scarce, decisions about adopting and providing coverage for breast cancer therapies are increasingly being made based on their "value for money" [2].

Undoubtedly, the incidence of invasive breast cancer has been steadily increasing since 2004.A new study has revealed that the increase in body mass index (BMI) and the decline in the average number of births per woman, both of which are known risk factors for breast cancer, have likely contributed to the recent surge in the prevalence of the illness. An estimated 231,840 women in the United States are projected to be diagnosed with breast cancer in 2017. Following lung cancer, breast cancer is the second leading cause of cancer-related deaths in women, making it a major factor in early mortality among women [3]. Early-stage breast cancer is often asymptomatic, making regular screening crucial for timely discovery and effective treatment. The predominant physical indication is an asymptomatic mass. Occasionally, breast cancer metastasizes to the lymph nodes in the underarm area, resulting in the formation of a lump or swelling. This can occur even before the primary tumor in the breast has grown to a size that can be detected by touch [4].

Serum indicators in breast cancer have the potential to be used for several purposes, such as assisting in early diagnosis, assessing prognosis, predicting response or resistance to certain medicines in advance, monitoring patients after primary surgery, and tracking the progress of therapy in patients with advanced illness [4].

This study aims to evaluate the diagnostic efficacy of tumor biomarkers (Serum P53, cathepsin D, cyclin E, and nestin) in distinguishing primary breast cancer from histopathological biopsy.

2 Material and methods

In this study, 60 women with breast cancer were enrolled. The age range of the study population was 30-74 years old. Thirty healthy women served as the study's control group. who made a visit to the Al-Sadr Teaching Hospital's Al-Basrah Oncology Center. The Al-Basrah Oncology Center at Al-Basrah Teaching Hospital provided the diagnosis for each patient included in this study under the supervision of specialized oncologist, which was then validated by a series of clinical and laboratory tests conducted between October 2020 and May 2020. The study's practical analyses were conducted at Southern Technical University's Medical Laboratory Technology department in Basrah., or enzyme-linked immunosorbent assay (ELISA), was utilized to assess nestin, cyclin E, cathepsin D, and serum P53.

2.1 Statistical analysis

The means ± standard deviation (SD) are used to express data. The chi-square test (for frequencies) and the t-test (for means) were used to compare differences between the groups. For all statistical studies, SPSS for Windows (version 23, USA) was used. One-way ANOVA for normally distributed data was employed. $P < 0.05$ was deemed statistically significant, whereas $P > 0.05$ was deemed non-significant.

3 Results

Table 1 displayed the age and breast cancer characteristics-related statistical distribution (frequency and percentage) of the study groups (patients and controls). According to this data, the age grouping with the largest proportion is those between the ages of 41 and 51, which made up 50% of the sick group and 5.7% of the control group. According to the same table, the patient subgroups with the highest percentages are Grade II (62.2%) and Stage II (68%).

Table 2 presented variations in serum biomarker measurements between the control group and BC patients. The following biomarkers had significantly higher levels (P value < 0.01) in the BC patients group as compared to the control group: Cyclin E and Nestin. The P53 levels in the BC patient group were significantly lower (P value < 0.01) than in the control group, according to the same data.

3.1 Measurement of biomarkers during different stages of breast cancer

The differences in biomarker readings across patient subgroups classified by stage of breast cancer were displayed in Table 3. This table demonstrates that there is a high significant rise (P value < 0.01) in Nestin levels and a high significant decline (P value < 0.01) in P53 levels in BC patients with stages IV and III compared to stage II. The information shows that BC patients with stage II had significantly higher levels of cyclin E (P value < 0.05) than patients with stages II and IV.

The areas under the curve (AUC) and receiver-operating characteristic (ROC) curve analysis of the biomarkers for breast cancer diagnosis were discussed in Table 4 and Figure 1. The sensitivity values for the markers Nestin, P 53, Cathepsin-D, and Cyclin E were, according to this table, 0.58%, 0.78%, 0.33%, and 0.43, respectively. The sensitivity values for the same markers were 0.40, 0.65, 0.20, and 0.33, according to the same table.

Table 1: Age and breast cancer characteristics-related statistical distribution (frequency and percentage) of research groups (Patients and controls).

Items	Sub-groups	BC Patients (N= 60)		Control Group (N= 30)		Chi Square (P value) Sig.
		Freq.	%	Freq.	%	
Age	30-40	11	18.3	4	13.3	2.05 (0.56) NS
	41-51	30	50.0	17	56.7	
	52-62	16	26.7	9	30.0	
	63-73	3	5.0	0	0.0	
Grade	I	0	0.0	-	-	-
	II	37	62.2	-	-	
	III	23	37.8	-	-	
	IV	0	0.0	-	-	
Stage	I	0	0.0	-	-	-
	II	45	75.6	-	-	
	III	12	20.0	-	-	
	IV	3	4.4	-	-	

NS : Non-significant at P value>0.05 ; SD : Standard Deviation

Table 2: Disparities in blood biomarker measurements between BC patients and the control group.

Biomarkers	BC Patients (N= 60)		Control Group (N= 30)		T Test P value
	Mean	SD	Mean	SD	
Nestin	409.01	196.24	279.33	135.85	4.02 0.000 HS
P 53	260.49	163.44	375.73	95.74	4.21 0.000 HS
Cathepsin - D	98.19	67.25	89.43	32.18	0.95 0.34 NS
Cyclin E	0.26	0.32	0.15	0.03	3.26 0.001 HS

HS: High Significant at P≤0.01; NS: Non-Significant at P≤0.05 ; SD: Standard Deviation

Table 3: Differences in the measurement of biomarkers found throughout the various stages of breast cancer are presented in the following ANOVA table.

Biomarkers		Stage Sub-groups			F Test P value
		Stage 2 (N= 45)	Sage3 (N= 12)	Stage4 (N= 3)	
Nestin	Mean	198.00 A	363.5 B	461.89 B	5.03
	SD	6.00	163.32	179.30	0.01 HS
P 53	Mean	668.50 A	282.94 B	252.35 B	8.65
	SD	279.29	159.23	187.49	0.000 false (0.007) HS
Cathepsin – D	Mean	89.96	120.00	139.90	2.29
	SD	36.56	128.76	60.45	0.11 NS
'Cyclin E	Mean	0.22 A	0.43 B	0.14 A	3.78
	SD	0.21	0.56	0.02	0.03 S

Table 4: Disparities in blood biomarker measurements between BC patients and the control group.

Biomarkers	BC Patients (N= 60)		Control Group (N= 30)		T Test P value
	Mean	SD	Mean	SD	
Nestin	409.01	196.24	279.33	135.85	4.02 0.000 HS
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Cathepsin - D	98.19	67.25	89.43	32.18	0.95 0.34 NS
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HS: High Significant at P≤0.01; NS: Non-Significant at P≤0.05 ; SD: Standard Deviation

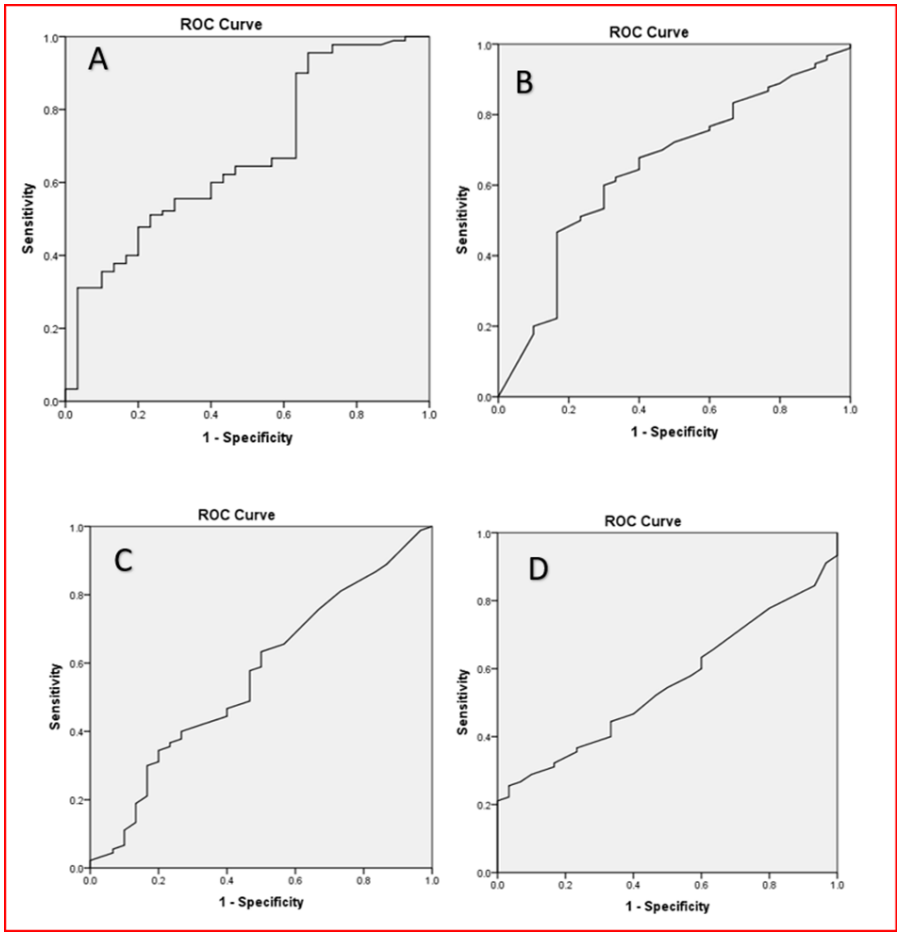

Figure 1: Diagonal segment of the ROC curve for (A) Nestin (B) : P 53 (C) : Cathepsin – D (D) Cyclin-E.

4 Discussion

The recent findings on Nestin align with a review undertaken by Nowak and Dziegiel [5]. They found that nestin expression was observed in the regenerative area of the normal human mammary gland, as well as in BC tumor cells. The role of nestin in the biology of CSCs has been examined by analyzing nestin expression in CSCs recovered from various types of human CNS tumors. Additional research has demonstrated that nestin is a valuable marker for identifying tumor cells that have characteristics similar to stem cells.

Within biological systems, cells exhibiting characteristics similar to stem cells may be distinguished by analyzing the arrangement of molecules on their outer surface. Specifically, these cells can be classified as CD44 antigen (CD44)+ and signal transducer CD24 (CD24)-/low based on their expression patterns. Subsequent research has shown that TN tumors and cell lines tend to have a significant presence of CD44+/CD24-/low cells, which is indicative of a negative prognosis and aggressive activity [6]. The findings of the present investigation contradict a prior study that reported significantly lower levels of serum Nestin in the breast cancer group compared to the control group [3].

Recent research have focused on nestin as a potential diagnostic and prognostic indicator of breast cancer. However, the role of nestin in breast cancer patients is still a subject of debate. Several studies have established a significant correlation between elevated nestin expression and worse prognosis in individuals with breast cancer. In contrast, several additional studies found no substantial correlation between the expression of nestin and the survival outcomes of patients with breast cancer. In addition to brain progenitor cells, nestin expression may also be observed in immature or progenitor cells in several normal organs. In normal breast tissues, nestin is specifically expressed in the basal/myoepithelial cells of the mammary gland [2].

In relation to cyclin-C, our results align with those of Kabel [7], who reported Cyclin E overexpression in a variety of cancer types, such as sarcomas, skin, lung, gastrointestinal, hematological, breast, and genitourinary tract cancers. Compared to normal human breast cells, Bi and his colleagues [8] discovered that in around 25% of breast cancers, Cyclin E is either abnormally stable or present at high levels. The results of this investigation are consistent with those of Mansouri and associates [9], who found that tumor samples expressed greater levels of Cyclin E, P21, and Ki-67 than did normal neighboring tissue. Furthermore, in comparison to normal human breast cells, cyclin E has been found to be either abnormally stable or present at high concentrations in around 25% of breast cancers [7]. It has been shown by a recent study that estrogen targets the genes cyclin E1 and cyclin E2. These genes are reported to be significantly expressed in breast cancer and may have a role in the development of resistance to anti-estrogen therapies. Breast tumors of the luminal B type that are ER+ have moderate expression of cyclin E1 mRNA, whereas basal-like breast cancers that are ER-negative exhibit the greatest level of expression [10]. A research found a high association between particular genetic abnormalities in the p53 tumor suppressor gene, such as insertions, deletions, and nonsense point mutations, and increased levels of cyclin E in breast cancers with p53 mutations [11].

The present study demonstrates a significant and substantial reduction (P value < 0.01) in the levels of P53 in the group of patients with breast cancer compared to the control group. The findings are consistent with the study conducted by Kamel et al. [12]. They examined fifty female patients with primary breast carcinoma or breast mass, aged between 17 and 78 years. The study revealed that the average level of serum p53 in women with breast cancer was 140.7 pg/mL $\pm$ 60.9 pg/mL, which was lower than that of healthy control women (192.6 pg/mL $\pm$ 285.5 pg/mL). The findings of Jabir and Hoidy [13] contradict our results. They reported mean TP53 concentration levels of 47+33.5 U/ml for patients with breast cancer and 27.8+12.7 U/ml for seemingly healthy individuals. However, they concluded that there was no significant difference between the two groups. The findings of the current investigation contradict the results of Hassan [14], who observed a substantial rise in total P53 levels in women with breast cancer compared to both healthy individuals and people with benign tumors.

Prior studies have indicated that the sensitivity and specificity of single marker detection of early metastatic disease following breast cancer surgery are restricted [15]. It was discovered that 39.9 pg/mL was the ideal threshold value for serum Nestin to differentiate between healthy people and breast cancer patients. The threshold that was set showed 84.8% sensitivity and 65.1% specificity in terms of diagnosis. The distribution of multiple alleles differed significantly between breast cancer patients and non-patients [3]. Nestin has been linked to the development of cancer stem cells and a poorer prognosis. It is thought to be a biomarker for the stem cell state. It is noteworthy to emphasize that endothelial cells and areas undergoing regeneration were thought to display significant levels of nestin. It has therefore been seen as a sign of angiogenesis and proliferation connected to cancers. However, a recent research by Dusart et al. cast doubt on the notion that Nestin is a marker of proliferation. They demonstrated in their study that employing siRNA to reduce Nestin expression actually caused endothelial cell proliferation to rise [16].

5 Conclusion

The study determined that Nestin and P53 had a comparatively high level of sensitivity and specificity in the detection of breast cancer. Furthermore, it may be inferred that these indicators have the potential to be employed in the detection of breast cancer.

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Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The study received ethical approval from Basrah University, Basrah, Iraq.

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