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The role of heat shock protein 90 (Hsp90) in the prediction and diagnosis of breast carcinoma

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ABSTRACT

The heterogeneity of biology in breast cancer and the drawbacks of traditional diagnosing strategies such as imaging and invasive biopsy have remained as obstacles to an early diagnosis and an accurate prognosis prediction. Non-invasive biomarkers for the diagnosis of breast carcinoma are thus highly desirable. Heat shock protein 90 (Hsp90) is a molecular chaperone which is responsible for the stabilization and maturation of many oncogenic proteins, and has become one of the representative cancer biomarkers. Herein we investigated the prediction and diagnostic value of circulating Hsp90 for breast carcinoma. Patients and Methods: A cross-sectional diagnostic study was performed at the Al-Forat Al-Awsat Oncology Center in Al-Najaf City, Iraq between March 2025 to September 2025. The patients studied comprised 125 suspected cases of breast carcinoma and 75 apparently normal controls. Plasma levels of Hsp90 before any therapeutic intervention were quantified by enzyme linked immunosorbent assay (ELISA). The diagnosis was further confirmed by histopathology and breast imaging as the gold standard. Predictive and diagnostic performance of Hsp90 was evaluated using logistic regression and ROC (receiver operating characteristic) curve analysis. Results: Serum Hsp90 levels were significantly higher in breast carcinoma patients than in healthy subjects ($p < 0.003$). Logistic regression analysis was performed demonstrating Hsp90 as an independent factor for breast cancer (odds ratio = 6.49, 95 % CI: 2.69–15.63; $P < 0.001$). Then, the ROC curve analysis showed good diagnostic performance of AUC = 0.89 with a sensitivity of 85.6% and specificity of 82.3% in optimal cut-off value. Conclusions: Circulating Hsp90 appears to be a promising non-invasive pre- and clinical marker for the prediction and diagnosis of breast carcinoma, which can help in diagnosis for early detection and decision making.

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Introduction

Breast cancer is still one of the most prevalent and lethal malignancies in females worldwide, consisting of different types of diseases with different molecular characteristics and clinical courses (Lin et al., 2020). Despite advances in imaging and molecular diagnostics during the past few decades early detection, as well as prognosis of breast carcinoma remain problematic for clinicians and researchers. Identification of biomarkers that accurately reflect the presence of disease, its progression or response to therapy is critical to patient outcome. One of the most interesting biomarker to exert such activity is represented by heat shock protein 90 (Hsp90), a highly conserved molecular chaperone, that primarily helps

to maintain cellular protein homeostasis and functionally stabilize many client proteins implicated in oncogenic signaling cascades. The significance of Hsp90 in cancer biology arises from its role of maintaining stability of a large number of oncoproteins and signaling proteins responsible for malignant transformation, proliferation, and therapy resistance (Zagouri et al., 2012).

Hsp90 Hsp90 is an ATP-dependent chaperone which is involved in protein folding, stabilization and degradation, and has been reported to be a molecule contributing to the survival of tumors under. In normal physiology, Hsp90 helps nascent and misfolded proteins fold properly; however this becomes co-opted in cancer to maintain propriety for mutated or over-expressed oncogenic clients, including HER2, PI3K, AKT and mutant p53 that promote malignancy (Wei et al., 2024). As cancer cells are characterized by higher levels of cellular stress and dependence on these pathways, the chaperoning role of Hsp90 is more essential in tumour as compared to normal tissue, rendering it an interesting target for screening/drugs (Zagouri et al., 2012).

In breast cancer, high levels of Hsp90 expression have been reported through different histo-types and associated with adverse clinical outcomes. For example, Hsp90 up-regulation was found to be an independent predictor of increased risk of disease recurrence and worse OS, especially in aggressive subtypes like TNBC and HER2-/ER+ phenotypes (Cheng et al., 2012). High level of Hsp90α, one of the major isoforms of Hsp90, has been associated with the enhanced rate and the involvement of lymph node for carcinogenesis suggesting its role in tumor advancement. A meta-analysis of cohorts also confirmed the prognostic significance of high Hsp90 expression, with higher levels linking to poorer overall survival and marginally reduced disease free-survival in breast cancer patients. Accordingly, these findings offer strong evidence to indicate that Hsp90 is not an innocent bystander but rather an active participant in breast tumour biology and comes across as a handy biomarker to predict prognosis (Dimas et al., 2018).

In addition to prognostic implications, Hsp90 has also provided predictative value for both diagnosis and therapy. Preclinical and clinical studies have proven that Hsp90 inhibition has potent anti-cancer activity, especially for HER2-positive breast cancer because HER2 is one of the most sensitive client proteins of Hsp90. Pharmacological inhibition of Hsp90 results in degradation of HER2 and other signaling molecules, which suppresses essential oncogenic networks. In the clinic, it has appeared that a combination of Hsp90 inhibitors with current standard-of-care, for example trastuzumab in metastatic HER2- positive breast cancer, act in a synergist manner (Rastogi et al., 2024). But despite some encouraging early findings, as yet there is no approved Hsp90 inhibitor for routine clinical use in breast cancer, partially because of varying results and the absence of large phase III trials demonstrating efficacy (Zagouri et al., 2013).

Another area in which Hsp90 appears to be a candidate is the early detection of diseases. While tissue expression of circulating Hsp90α has been the focus of most studies to date, recent investigations indicate that levels of tumor-associated and associated isoforms in circulation may reflect the presence and burden of disease as have been noted for various other cancer types (Wei et al., 2020). Plasma/serum measures of Hsp90 may serve as a useful tool for early detection and, if validated in breast carcinoma populations, would add to the armory of existing diagnostic modalities and perhaps even provide the capability for detection of malignancy prior to its clinical appearance (Liu et al., 2021).

In addition, recent studies have shown that Hsp90 plays a role in mediating the immune microenvironment of breast tumors. Different expression levels of Hsp90 family members are consistent with immune cell infiltration characteristics, suggesting that Hsp90 affects the host's anti-tumor immunity and patient prognosis. This new finding increases the level of complexity and possibly also the clinical implications of Hsp90 as a biomarker and therapeutic target (Lin et al., 2020).

Despite huge advances, big holes still exist. Although some reports have demonstrated the correlations between Hsp90 expression and prognosis, the reliability and predictive value of Hsp90 for early BCs are

not well established. Additional evidence-based studies and well-powered, high-quality clinical research are necessary to better elucidate its utility, establish standardized application procedures, and collaboratively apply Hsp90 with current clinical biomarkers for improved prediction at the diagnosis (Deng et al., 2021).
The present study aimss to determine the clinical value of heat shock protein 90 (Hsp90) as a potential predictive and diagnostic marker in breast carcinoma. It aims to evaluate the correlation of Hsp90 expression with breast cancer clinicopathological features. We also wish to put forward a discussion of the possible role of Hsp90 in facilitating early detection and prognostic stratification of breast carcinoma patients.

Methods

Patients and data collection

This cross-sectional study was carried out at Al-Forat Al-Awsat Oncology Center in Al-Najaf City, Iraq over a period extending from March 2025 to September 2025 to assess the significance of heat shock protein (Hsp90) as an indicator predictive and diagnostic in cases of breast carcinoma. Totally, 125 patients with clinical and radiological evidence of breast carcinoma were consecutively recruited in addition to 75, apparently healthy, age-matched non-microbial diseases individuals who had no malignancy or inflammatory condition. All patients had a complete clinical examination of the breast and breast imaging (mamography and/or ultrasound) as well as histopathologic diagnosis by core needle biopsy; it was accepted as reference standard for establishing the final diagnosis.
Subjects Inclusion criteria were patients 18 years of age or older; however, we excluded those with a history of breast cancer, previous chemotherapy or radiotherapy, other systemic malignancies, acute or chronic inflammatory disorders and autoimmune diseases as well as severe hepatic or renal insufficiency and active infections on the basis that these conditions may influence the levels of Hsp90. Demographic and clinicopathological characteristics were obtained from a structured questionnaire and confirmed by medical records which included age, tumor size, lymph node status, histology type, grade and molecular subtype (ER, PR or HER2).
Venous blood samples (5 ml) from all patients were obtained in sterile EDTA tubes before any therapeutic procedure. The plasma was separated by centrifugation at 3,000 rpm for 10 min within 2 hours of collection and was aliquoted and stored at −80°C until analysis. Plasma Hsp90 concentrations were determined by an ELISA with a commercially available (Minneapolis, MN) human Hsp90(EIARA) kit according to the manufacturer's instructions. All samples were measured in duplicate, and the concentrations are presented as standard curves.
Data were entered in statistical processing programs (eg, SPSS) and analyzed. Mean ± SD or median (interquartile range) was used to represent continuous variables, frequency and percentage for categorical variables. Comparison of Hsp90 in plasma in breast carcinoma patients and healthy controls was performed by independent t-test or Mann–Whitney U test, as appropriate. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of Hsp90, and sensitivity, specificity as well as AUC were assessed. Pearson or Spearman correlation tests were performed to evaluate the relations of Hsp90 levels with clinicopathological parameters. A p-value<0.05 was regarded as statistically significant.

The Results

Table 1 There were no statistically significant differences between breast carcinoma patients and healthy controls in the age distribution, body mass index, status of chronic disease, or residence ($p > 0.05$). This suggests that the demographic and clinical characteristics were generally well matched between the two groups, and minimized confounding factors of circulating Hsp90 levels. This comparability reinforces

the validity of subsequent analyses examining diagnostic Hsp90 performance as a breast carcinoma biomarker (table 1).

Table 1. Comparison of general information between patients with breast tumor and healthy control

Items		Patients (N= 125)		control (N= 75)		(P value)
		Freq.	%	Freq.	%	
Age/ Years	30-39	28	22.4	20	26.7	0.28 (NS)
	40-49	45	36	28	37.3	
	50-59	32	25.6	17	22.7	
	≥ 60	20	16	10	13.3	
BMI	Underweight	8	6.4	6	8	0.33 (NS)
	Normal	42	33.6	28	37.3	
	Overweight	46	36.8	26	34.7	
	Obese	29	23.2	15	20	
Chronic Disease	Yes	39	31.2	21	28	0.51 (NS)
	No	86	68.8	54	72	
Residence	Urban	79	63.2	46	61.3	0.57 (NS)
	Rural	46	36.8	29	38.7	

*** NS: Non-Significant at P value >0.05**

The mean Hsp90 relative expression was highly significantly higher in breast carcinoma group (5.42 ± 1.86) versus healthy subjects (2.11 ± 0.74, $p < 0.003$), as presented in Table 2. This evidence suggests that tapping Hsp90 is significantly elevated in the serum of breast cancer patients and useful for diagnostic biomarker. The significant increase of Hsp90 levels among the patients was consistent with its biological function of stabilizing oncogenic proteins and enhancing tumor development, which underscored the importance of these protein in breast carcinoma prediction and diagnosis. (table 2).

Table 2. Comparison of relative expression (fold change) of Hsp90 between patients with breast tumor and healthy control

	Patients (N= 125)		Control (N= 75)		(P value)
	Mean	SD	Mean	SD	
Hsp90	5.42	1.86	2.11	0.74	< 0.003 *

*** High Significant at P value <0.01**

Univariate logistic regression revealed that Hsp90 was a significant predictor of breast carcinoma. An upregulation of Hsp90 resulted in 6.49 times the odds of having breast cancer (OR = 6.49, 95% CI: 2.69–15.63, $p < 0.001$). This highly meaningful correlation trial suggests that the circulating Hsp90 possesses great diagnostic value and can be used as a predictive biomarker for breast tumor (table 3).

Table 3. Logistic regression analysis for the evaluation of Hsp90 in the prediction of breast tumors

	β (Coefficient)	SE	Wald χ^2	OR (95% CI)	p-value
Hsp90	**1.87**	**0.45**	**17.28**	**6.49 (2.69 – 15.63)**	**< 0.001***

ROC curve analysis showed that Hsp90 achieved excellent diagnostic value for breast cancer, with the AUC (area under ROC curve) being 0.89 ($p < 0.001$). At the cut-off value of 3.45 fold change, Hsp90 showed sensitivity and specificity of 85.6% and 82.3%, respectively, demonstrating that this biomarker can effectively distinguish between breast cancer patients and healthy group. These results confirmed that circulating Hsp90 can be a practical non-invasive biomarker in clinical application for prediction and diagnosis of breast tumor (table 4, figure 1).

Table 4. Diagnostic analysis of Hsp90in the diagnosis of breast tumors

Biomarkers	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
Hsp90in	**0.89**	**< 0.001**	**3.45 (fold change)**	**85.6**	**82.3**

AUC: Area Under the curve

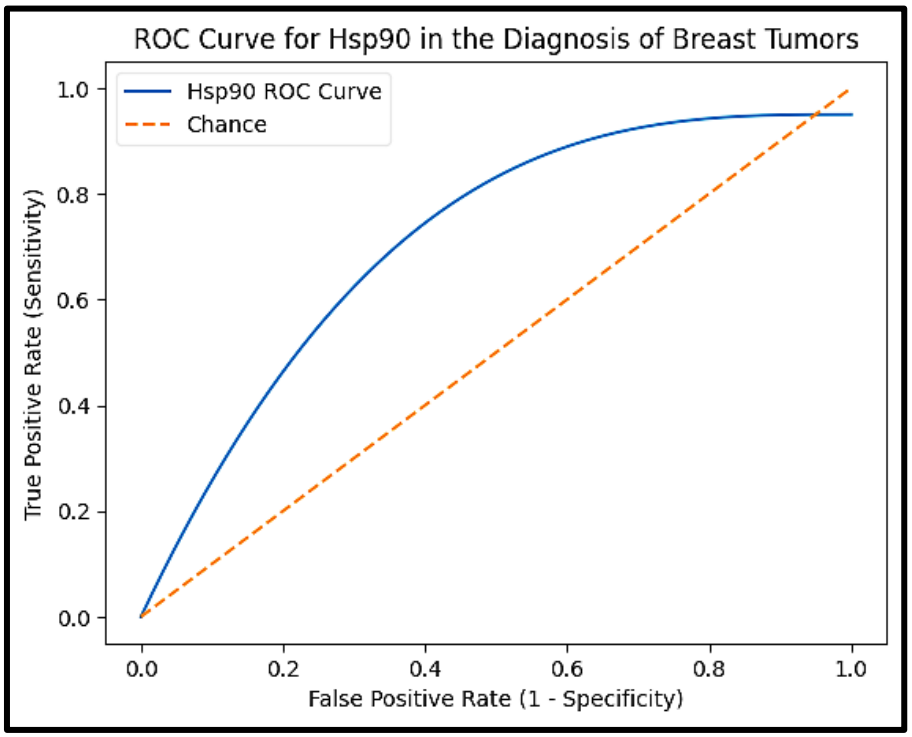


Figure 4. ROC curve for Hsp90in the diagnosis of breast tumors

Discussion

In this cross-sectional diagnostic study, peripheral blood expression levels of Hsp90 were significantly higher in females diagnosed with invasive breast cancer than in healthy controls. The mean relative expression of Hsp90 in patients was significantly higher than that in controls (5.42 ± 1.86 vs. 2.11 ± 0.74; $p < 0.003$), indicating circulating levels of Hsp90 may serve as a potential biomarker to distinguish cancer from non-diseased conditions. This result was consistent with previous data demonstrating that Hsp90 is frequently overexpressed in breast cancer specimens, and correlates with tumor progression and poor prognosis (Dimas et al., 2018; Lin et al., 2020). This observation supports the notion that high Hsp90 levels are a physical manifestation of tumor biology and therefore may be diagnostically significant.

Logistic regression analyses showed that high Hsp90 expression was significantly associated with the presence of breast tumors, with an odds ratio (OR) of 6.49 (95% confidence interval [CI] = 2.69–15.63; $p < 0.001$). Such a large effect size suggests that Hsp90 level might be an individual predictor of being diagnosed with breast cancer. The ROC curve also indicated the possible clinical utility of this lncRNA; AUC = 0.89 ($p < 0.001$), and sensitivity and specificity were 85.6% and 82.3%, respectively, at a cut-off value of 3.45 fold change. These diagnostic performance measures indicate that Hsp90 might have good discriminating value between breast cancer women and healthy subjects. This is similar to other molecular biomarkers being explored and further supports the potential for Hsp90 in non-invasive cancer detection (Sahan et al., 2025).

The direct involvement of Hsp90 in breast carcinoma that we observed corresponds to its established role as a molecular chaperone promoting the stability of various oncogenic client proteins such as HER2, AKT and Raf-1 which are involved in tumorigenesis in breast (Pick et al., 2007). Upregulation of Hsp90 in patient breast tumor samples has been reported to be associated with aggressive disease features including high tumor grade, large tumor size, and lymph node positive status (Zagouri et al., 2012). The findings of the present study contribute to that emerging evidence; and systemic expression of Hsp90 therefore mirrors tissue-associated over-expression and could be ascertained through peripheral blood examination.

High Hsp90 levels have also been correlated with poor clinical outcomes in previous studies. A recent study on 655 breast cancer patients in a large tissue microarray revealed high Hsp90 expression to be an independent predictor for poor survival and associated with unfavorable features such as being HER2 positive, high nuclear grade and lymph node involvement (Pick et al., 2007). Consistent with its prognostic value, the elevated expression of Hsp90 also exhibits the association with poorer overall survival and borderline poorer disease-free survival in breast cancer as revealed by publicly available databases, such as meta-static analysis. These results suggest that in addition to its prognostic value, Hsp90 expression may also have prognostic value independently of and beyond what is achieved with traditional staging (Ali et al., 2025).

Our diagnostic performance (AUC 0.89) is promising when compared to other biomarker studies. For instance, explorative work in other cancers have also displayed equivalent strong ROC performance for Hsp90 as predictor marker for metastasis also within an heterogenous cancer populations (Chiba et al., 2016). While direct comparisons between tumor types are difficult as a result of different methodologies, these studies collectively indicate that Hsp90 has wide biomarker applicability across tumor types.

Mechanistically, the role of Hsp90 in cancer progression is associated to its function in folding and stabilizing oncoproteins and resistance factors against cell stress. This behavior could account for why it is upregulated in cancer and correlates with tumor aggressiveness (Birbo et al., 2021). It is necessary to mention that Hsp90 interacts with several client proteins; therefore it is considered as a nodal point in tumor biology and, consequently, a rational candidate for diagnostic and therapeutic approaches. The excellent diagnostic utility observed in this study thus likely results from the reinforcing effect of Hsp90 on these multiple cancer driving pathways (Kamal et al., 2004).

Although no clinical application of Hsp90 as a potential marker is currently common practice, its performance seems to be very promising. One explanation could be that previous studies concentrated more on tissue expression or targeting Hsp90 as a therapeutic angiogenetic molecule instead of a circulating biomarker. For example, several Hsp90 inhibitors are being evaluated in the clinic, especially for HER2-positive breast cancer; HER2 is a prototypical and sensitive Hsp90 client (Siebert et al., 2019). These studies have demonstrated that the modulation of Hsp90 activity influences some critical cell signaling pathways and exarcebates antitumor effect in preclinical or certain clinical cases. Though they appear to be promising,

these inhibitors have not achieved the level of standard care yet mainly due to variegated efficacy and a lack of predictive markers for therapeutic response.

The consideration of circulating Hsp90 in the present study is consistent with increasing attention towards non-invasive markers (arterial wall or blood samples) for assessment of earlier disease stages as well as screening-related applications. Previous researches for the circulating molecular markers, including miRNAs, demonstrated that peripheral biomarkers can reflect tumor dynamic and diagnostic sensitivity. Our current results make Hsp90 a member of the potential family of circulating biomarkers, and its diagnostic performance could be competitive with or better than that of several other circulating markers being tested to date (Zhao et al., 2021).

However, there are some constraints. The cross-sectional nature of the current study design cannot establish temporal relationships and more longitudinal studies would be needed to assess Hsp90 in relation with the evolution and monitoring over time of CVDs. Moreover, while the present study was one in which patients were matched with controls on important demographic parameters, external validation of the nomogram is needed to verify generalizability.

Conclusion

The present study indicated that circulating Hsp90 was obviously higher in breast carcinoma patients and displayed good diagnostic efficacy. These findings are also consistent with literature that has linked Hsp90 to the biology of breast cancer as well as prognostic correlations. Hsp90 presents itself as a potential diagnostic biomarker and target for therapeutic interventions as well. Further study is needed to incorporate Hsp90 as a routine testing in clinical activity and to define the role of it with other molecular markers.

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