

Serum HSP-70 and XBP-1 as Diagnostic and Treatment-Monitoring Biomarkers in Breast Cancer

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Abstract

Introduction: To lower breast cancer mortality, clinicians need non-invasive biomarkers for earlier detection and evaluating disease status. HSP-70 controls protein folding and XBP-1 directs the unfolded protein response (UPR). Tumors exploit these dysregulated pathways for survival and drug resistance. We tested serum HSP-70 and XBP-1 as markers for diagnosis and chemotherapy response. **Methods:** The study included 90 women, ages 30 to 65, from the Anbar Governorate for a cross-sectional comparison. This study included 30 newly diagnosed breast cancer patients (Group A), 30 patients undergoing chemotherapy (Group B), and 30 age-matched healthy controls (Group C). ELISA measured serum concentrations of HSP-70 and XBP-1. We used Kruskal-Wallis, Mann-Whitney U, PCA, and ROC curve analyses to evaluate biomarker performance. **Results:** Newly diagnosed patients showed elevated serum levels of both biomarkers compared to healthy and treated groups. Group A showed higher mean HSP-70 and XBP-1 levels (1.91 ng/ml and 146.84 pg/ml) than the control group (1.19 ng/ml and 120.91 pg/ml, $p < 0.001$). Chemotherapy patients (Group B) had lower levels of HSP-70 (1.41 ng/ml) and XBP-1 (110.28 pg/ml) than the newly diagnosed group. HSP-70 (AUC = 0.969) and XBP-1 (AUC = 0.814) distinguished newly diagnosed patients from controls. The two markers correlated positively ($r = 0.52$). **Conclusion:** Serum HSP-70 and XBP-1 levels are elevated in newly diagnosed breast cancer and appear lower in patients undergoing chemotherapy. Together, they show potential as an indicator panel for disease status, though longitudinal studies are required to confirm their utility in dynamic treatment monitoring.

Keywords: Breast cancer, Chemotherapy, XBP-1, HSP-70, Cancer Diagnostics

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Introduction

High breast cancer mortality rates demand new biomarkers to improve early detection and treatment [1-4]. Cancer frequently dysregulates the expression of heat shock proteins (HSPs), which are molecular chaperones that maintain cellular homeostasis. Overexpression of the protein folding chaperone HSP-70 contributes to the pathogenesis of breast and other cancers. Higher HSP-70 levels promote tumor progression and therapy resistance. Its overexpression confers anthracycline resistance in breast cancer [5-10].

The accumulation of unfolded or misfolded proteins in the endoplasmic reticulum triggers the unfolded protein response (UPR) [11-15]. The UPR transcription factor X-box binding protein 1 (XBP-1) promotes tumor growth

and survival upon activation. Cancer cells overexpress spliced XBP-1 (XBP-1s), promoting drug resistance. The transcription factor XBP-1s activates genes that restore protein-folding homeostasis and promote cell survival under stress. This mechanism drives tamoxifen resistance in estrogen receptor-positive breast cancer and is also found in hepatocellular carcinoma and multiple myeloma [16-22].

HSP-70 and XBP-1 help cancer cells survive stress, suggesting their combined value as a serum biomarker. How these factors interact within the tumor microenvironment remains unknown, though each independently promotes cancer progression. Hypoxia and nutrient deprivation trigger therapeutic resistance and

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activate two pathways that promote cancer cell adaptation [23, 24]. A combined biomarker panel for the heat shock and unfolded protein responses better predicts tumor status and treatment outcome.

We hypothesize that serum HSP-70 and XBP-1 levels are higher in breast cancer patients than in healthy individuals and that chemotherapy alters these levels. We compared serum biomarker concentrations among newly diagnosed breast cancer patients, patients receiving chemotherapy, and healthy controls. We assess the diagnostic accuracy of HSP-70 and XBP-1. We also test a wider biomarker panel to stratify patients, guide diagnosis, and monitor chemotherapy response.

Materials and Methods

Study Design and Participants

We compared 90 women aged 30 to 65 from Anbar Governorate in a cross-sectional study. The study included three groups of 30 women. These groups were newly diagnosed breast cancer patients (Group A), patients receiving chemotherapy (Group B), and age-matched healthy controls (Group C). We designed the experiment as shown (Figure 1).

Sample Collection and Biomarker Measurement

We isolated participant serum and stored it at -20°C pending analysis. We quantified serum concentrations of XBP-1 and HSP-70 with a commercial ELISA kit. Spectrophotometry quantified total protein and albumin. We measured age, weight, height, Body Mass Index (BMI), and levels of the tumor marker CA 15-3. We quantified serum concentrations of XBP-1 (specifically

targeting the total XBP-1 isoform) and HSP-70 using commercial ELISA kits (Sunlong Biotech, China; Catalog numbers SL3099Hu for XBP-1 and SL0831Hu for HSP-70). The limits of detection for the assays were 0.1 ng/ml for HSP-70 and 5 pg/ml for XBP-1, according to the manufacturer's protocols.

Statistical Analysis

We used Python v3.11 with the Pandas, SciPy, and Scikit-learn libraries for all statistical analyses. We summarized variables by their mean, median, and standard deviation. Non-normally distributed data required the Kruskal-Wallis test for group comparisons. We used the Mann-Whitney U test for pairwise group comparisons. Biomarker profiles separated the groups in a Principal Component Analysis (PCA). Receiver Operating Characteristic (ROC) analysis and Area Under the Curve (AUC) values established the biomarker's sensitivity and specificity for separating patients from controls. To evaluate the combined diagnostic power of HSP-70 and XBP-1, a logistic regression model was utilized to create a combined multi-marker panel, which was subsequently evaluated using ROC curve analysis.

Results

Participant Demographics and Baseline Characteristics

The study groups differed in biomarkers and demographics (Table 1). The groups were similar in age ($p=0.4984$, Figure 2). Although the overall BMI difference among groups was not significant ($p=0.1165$), newly diagnosed patients had a higher BMI than patients undergoing chemotherapy ($p=0.0406$, Figure 3). Albumin

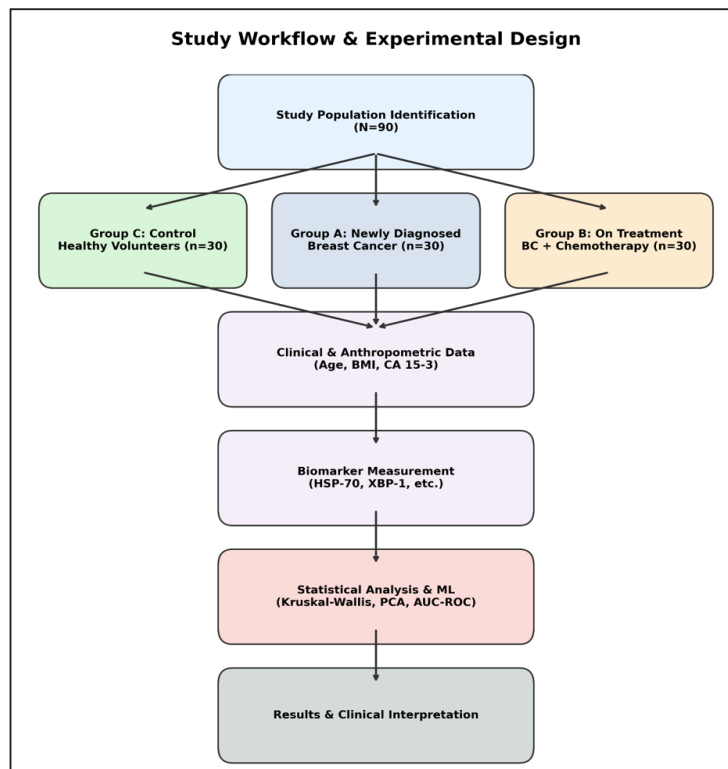


Figure 1. Study Workflow and Experimental Design. We recruited and grouped participants for subsequent data collection and analysis.

($p=0.00087$), Total Protein ($p=0.00205$), and the tumor marker CA 15-3 showed significant differences. Compared to controls, the newly diagnosed group had significantly lower albumin levels ($p=0.0008$).

Serum Biomarker Levels are Significantly Altered in Breast Cancer Patients

Newly diagnosed breast cancer patients (Group A) showed significantly higher mean HSP-70 levels at 1.91 ng/ml compared to 1.19 ng/ml in the control group (Group C) (Figure 4). The chemotherapy group (B) averaged 1.41 ng/ml of HSP-70. The mean XBP-1 level was higher in Group A (146.84 pg/ml) than in Group C (120.91 pg/ml) (Figure 5). XBP-1 levels in Group B averaged 110.28 pg/ml.

HSP-70 ($p=1.8944e-10$) and XBP-1 ($p=5.7987e-07$) levels differed significantly among the three groups (Kruskal-Wallis). Pairwise comparisons using the Mann-Whitney U test showed that the levels of HSP-70 and XBP-1 were significantly higher in newly diagnosed patients (Group A) compared to the control group (Group C) ($p=0.0000$ for both). Furthermore, patients undergoing chemotherapy (Group B) had significantly lower levels of both HSP-70 and XBP-1 compared to newly diagnosed patients (Group A) ($p=0.0000$ for both). The chemotherapy group also showed significantly higher HSP-70 levels compared to the control group ($p=0.0156$).

Table 1. Summary Statistics of Biomarkers

Biomarker	Statistic	Group A (Newly Diagnosed)	Group B (On Chemo)	Group C (Control)
HSP-70 (ng/ml)	Mean	1.91	1.41	1.19
	std	0.37	0.31	0.27
	Median	1.83	1.45	1.19
XBP-1 (pg/ml)	Mean	146.84	110.28	120.91
	std	29.44	21.29	15.15
	Median	139.24	111.62	118.12

Table 2. Area Under the Curve (AUC) for Biomarkers in Diagnosing Breast Cancer (Group A vs. Group C)

Biomarker	AUC
HSP-70	0.969
XBP-1	0.814
CA 15-3	1
Albumin	0.811
Total Protein	0.575
BMI	0.593
Age	0.531

Levels of the established marker CA 15-3 were, as expected, significantly elevated in both patient groups (A and B) compared to the control group C ($p=0.0000$ for both), with mean values of 42.93 U/ml and 40.63 U/ml, respectively, versus 15.75 U/ml in controls (Figure 6). Albumin levels (g/dl) were significantly lower in Group A compared to both Group B ($p=0.0023$) and Group C ($p=0.0008$) (Figure 7). Total protein (g/dl) was significantly lower in the chemotherapy group (Group B) compared to both the newly diagnosed group ($p=0.0062$) and the control group ($p=0.0014$) (Figure 8).

HSP-70 and XBP-1 Demonstrate Strong Diagnostic Potential for Breast Cancer

We used ROC curve analysis to measure biomarker diagnostic performance. AUC values distinguish newly diagnosed patients (Group A) from controls (Group C) (Table 2, Figure 9). HSP-70 demonstrated excellent diagnostic accuracy with an AUC of 0.969. XBP-1 also showed good diagnostic potential with an AUC of 0.814. When evaluated together as a combined predictive panel using logistic regression, the diagnostic accuracy improved, yielding a combined AUC of 0.975. The established tumor marker CA 15-3 had a perfect AUC of 1.000 in this comparison; however, a detailed data audit revealed this is due to complete mathematical

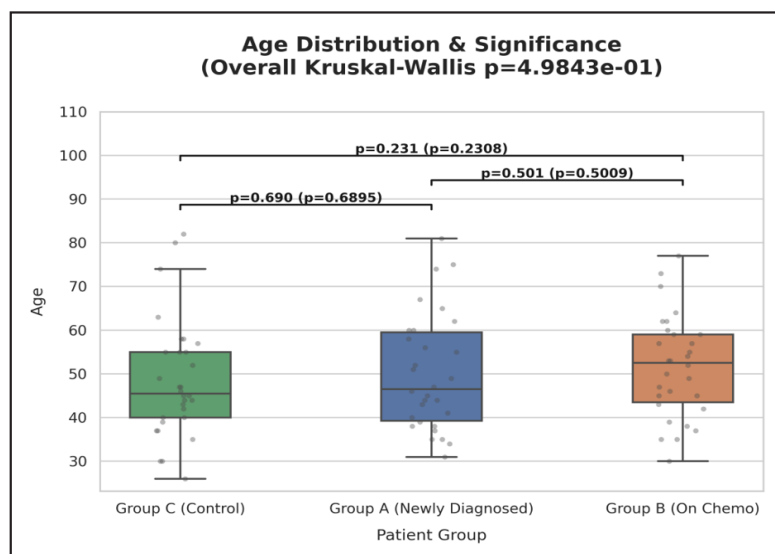


Figure 2. Age Distribution. Age distribution among the Control (Group C), Newly Diagnosed (Group A), and On Chemo (Group B) groups. The groups did not differ significantly ($p=0.4984$).

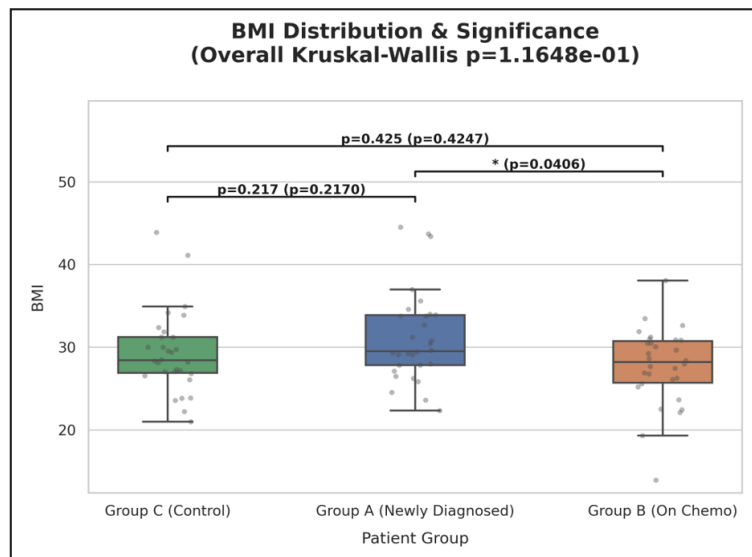


Figure 3. BMI Distribution. Body Mass Index (BMI) varied across the three study groups. The overall difference was not significant ($p=0.1165$).

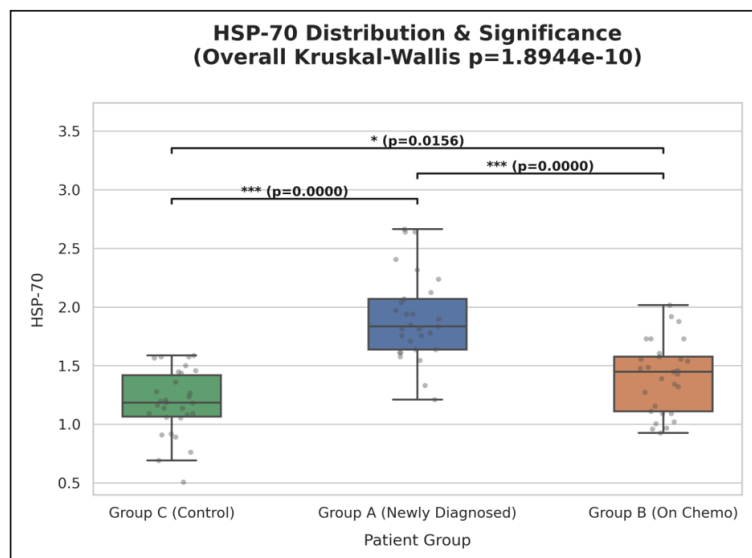


Figure 4. HSP-70 Distribution. Boxplot illustrating the serum levels of HSP-70. Levels were significantly higher in newly diagnosed patients (Group A) compared to controls (Group C) and patients on chemotherapy (Group B).

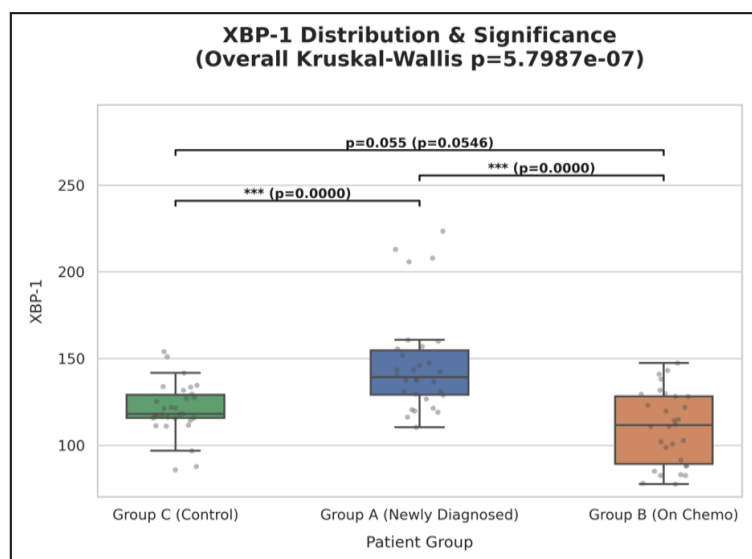


Figure 5. XBP-1 Distribution. Boxplot showing the serum levels of XBP-1. Levels were significantly elevated in the newly diagnosed group (A) compared to the other two groups.

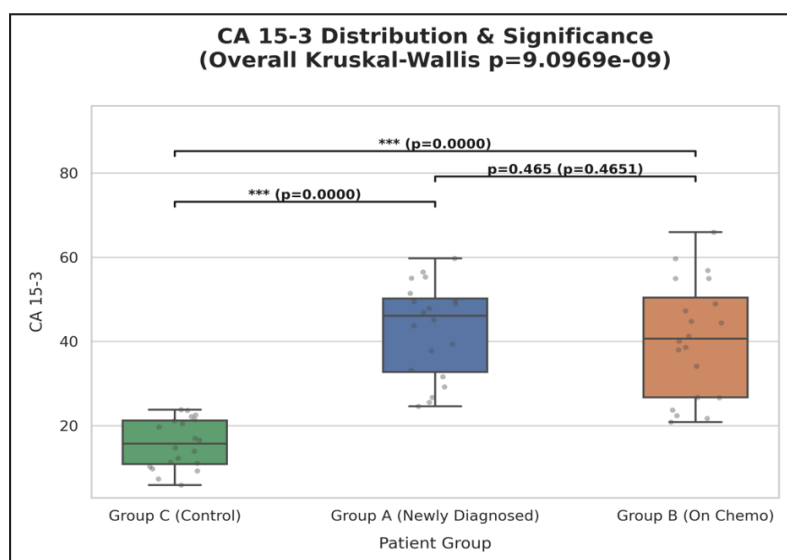


Figure 6. CA 15-3 Distribution. Boxplot of the tumor marker CA 15-3, showing significantly elevated levels in both patient groups (A and B) compared to the control group (C).

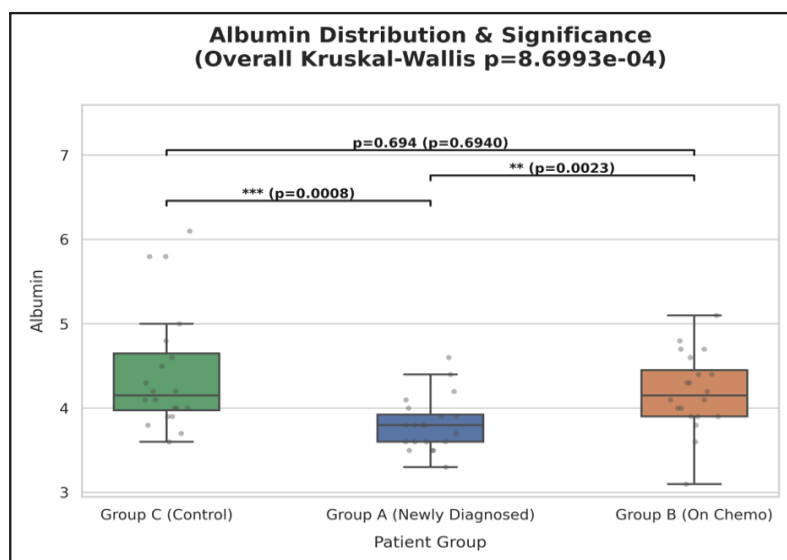


Figure 7. Albumin Distribution. Boxplot showing significantly lower serum albumin levels in the newly diagnosed group (A) compared to controls (C) and patients on chemotherapy (B).

discrimination within our specific cohort with no overlap, as the highest control value was 23.84 U/ml and the lowest newly diagnosed patient value was 24.65 U/ml (a gap of 0.81 U/ml). Albumin also showed good performance with an AUC of 0.811. For the comparison between patients on chemotherapy (Group B) and controls (Group C), the AUC for HSP-70 was 0.684, and for XBP-1, it was 0.645, indicating a reduced but still present discriminatory ability (Figure 10). When utilizing the combined predictive panel for this comparison, the combined AUC was 0.770. In this comparison, CA 15-3 maintained excellent performance (AUC = 0.965), and Total Protein showed good discriminatory ability (AUC = 0.795).

Biomarker Profiles Differentiate Patient Groups and Reveal Key Correlations

PCA was performed to visualize the overall separation of the patient groups based on their biomarker profiles. The first two principal components (47.4% of total variance)

separated newly diagnosed patients (Group A), patients on chemotherapy (Group B), and controls (Group C) (Figure 11). HSP-70 correlated positively with XBP-1 ($r = 0.52$, $p < 0.001$) (Figure 12). HSP-70 positively correlated with CA 15-3 ($r=0.49$, $p<0.001$). Analysis of the variable loadings revealed that the separation along the first principal component (PC1) was primarily driven by HSP-70 (loading = 0.600) and CA 15-3 (loading = 0.528). Conversely, the second principal component (PC2) was largely influenced by Total Protein (loading = 0.658) and XBP-1 (loading = 0.647), Figure S1.

Discussion

Our investigation reveals a compelling narrative: the serum concentrations of two key stress-response proteins, HSP-70 and XBP-1, are significantly elevated in women newly diagnosed with breast cancer and are subsequently reduced in patients undergoing chemotherapy. This

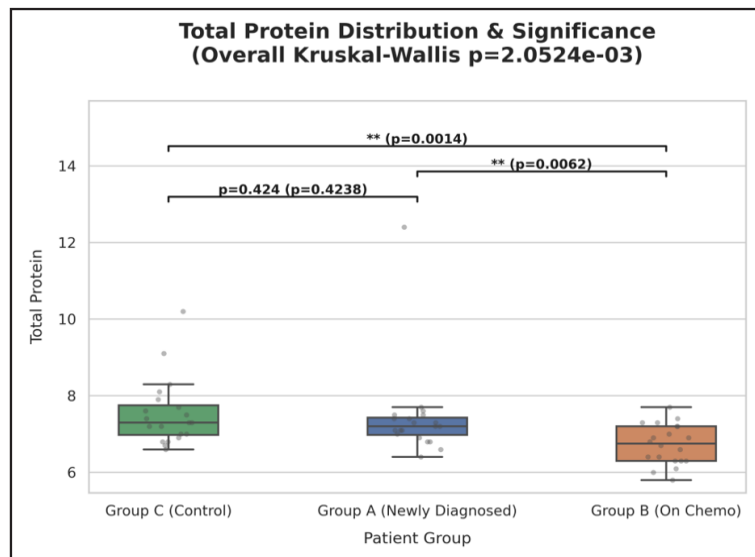


Figure 8. Total Protein Distribution. Boxplot showing the distribution of total protein, with lower levels observed in the patient groups compared to controls.

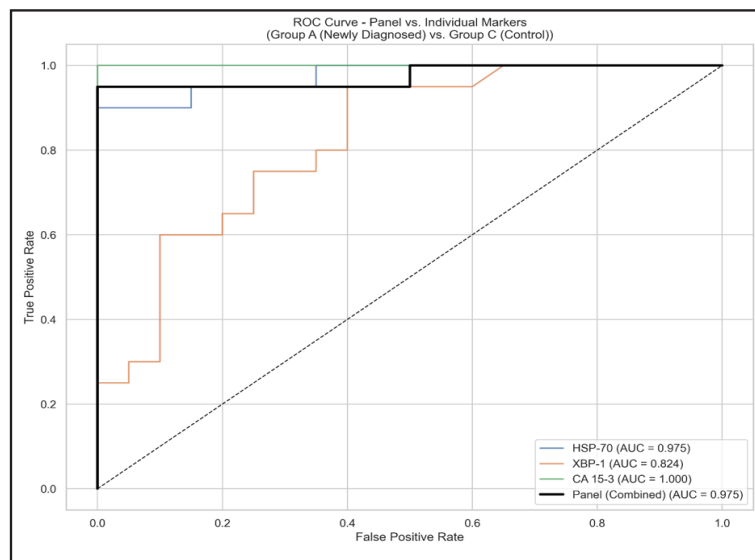


Figure 9. ROC Curve for Group A vs C. Receiver Operating Characteristic (ROC) curves for distinguishing newly diagnosed patients (Group A) from controls (Group C).

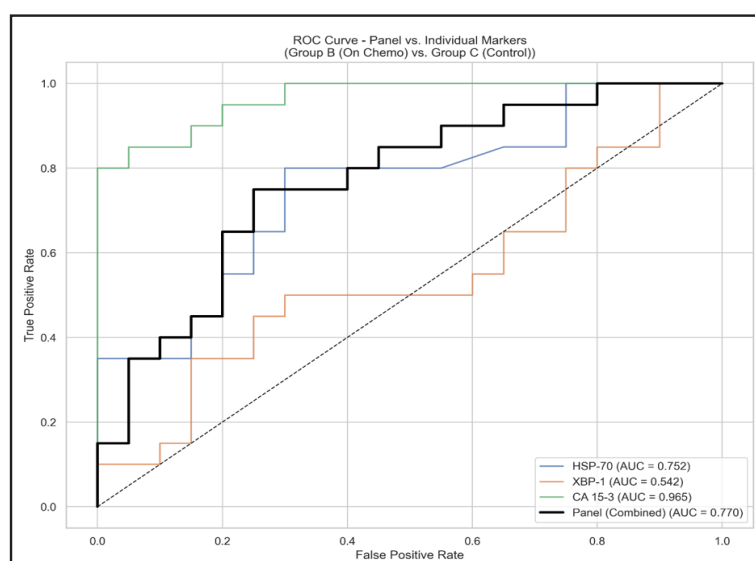


Figure 10. ROC Curve for Group B vs C. ROC curves for distinguishing patients on chemotherapy (Group B) from controls (Group C).

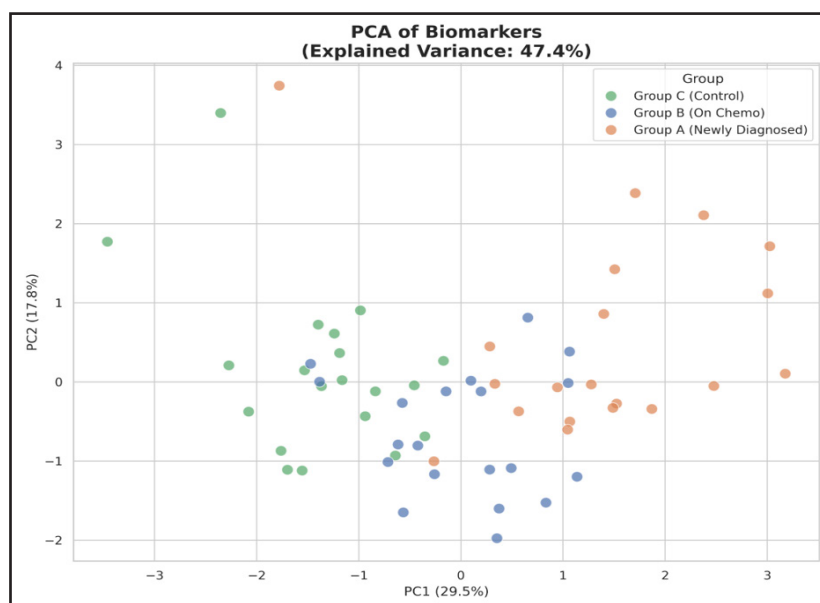


Figure 11. PCA of Biomarkers. Principal Component Analysis (PCA) plot showing the separation of the three study groups based on their overall biomarker profiles. The first two principal components explain 47.4% of the variance.

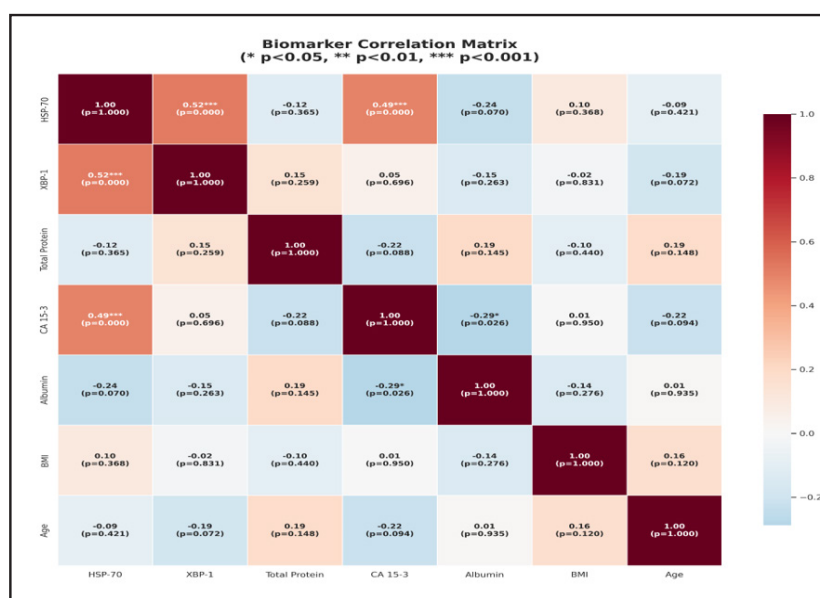


Figure 12. Biomarker Correlation Matrix. Heatmap showing the Pearson correlation coefficients between the measured biomarkers. A significant positive correlation was observed between HSP-70 and XBP-1 ($r=0.52$, $p=0.000$).

finding strongly supports our hypothesis and positions these molecules as promising, non-invasive biomarkers that reflect the underlying biology of the disease and its response to therapeutic intervention [25, 26]. XBP-1 pathway activation, an element of the unfolded protein response, promotes tumorigenesis and drug resistance [27–30].

The exceptional diagnostic performance of HSP-70, with an AUC of 0.969, underscores its potential as a powerful tool for discriminating between healthy individuals and those with nascent malignancy [31]. The biological rationale for these observations is rooted in the fundamental mechanisms of tumorigenesis. Cancer cells, characterized by rapid proliferation and metabolic reprogramming, exist in a state of constant proteotoxic stress. To survive, they hijack and upregulate cellular

machinery designed to manage this stress. HSP-70, a canonical molecular chaperone, is a central player in this process. Its overexpression protects cancer cells from apoptosis, stabilizes oncogenic proteins, and facilitates the folding of the vast quantities of new proteins required for growth, thereby promoting tumor progression and metastasis. The presence of elevated HSP-70 in the serum is a direct reflection of this intracellular upregulation, as stressed and dying tumor cells release their contents into the bloodstream. Similarly, XBP-1 is a critical transcription factor in the unfolded protein response (UPR), a pathway activated by the accumulation of misfolded proteins in the endoplasmic reticulum a common feature of secretory and rapidly growing cancer cells. The active, spliced form of XBP-1 (XBP-1s) orchestrates a transcriptional program that expands the cell's protein-folding capacity, enhances

survival under hypoxic or nutrient-deprived conditions, and contributes to therapy resistance. Thus, the elevated serum levels of HSP-70 and XBP-1 are not arbitrary markers but are direct readouts of the core adaptive stress responses that enable malignant survival [32].

Our findings align with and extend previous work in the field. Studies have consistently reported that serum HSP-70 is a valuable biomarker in breast cancer. For instance, one study found significantly higher serum HSP-70 in breast cancer patients (5.98 ng/ml) compared to healthy controls (1.49 ng/ml), demonstrating high sensitivity and specificity. Another investigation in Egyptian women with breast cancer confirmed that serum HSP-70 was over-expressed and correlated with advanced disease, including tumor size and metastasis. Our observed mean HSP-70 level of 1.91 ng/ml in newly diagnosed patients is within the range of these prior reports and reinforces its diagnostic utility. Our study, however, is one of the first to concurrently measure serum XBP-1, a key component of the distinct but related UPR pathway. The positive correlation we observed between HSP-70 and XBP-1 ($r=0.52$) hints at a coordinated biological response, where cancer cells engage both the cytosolic heat shock response and the endoplasmic reticulum-based UPR to manage proteotoxic stress. Tellingly, our principal component analysis revealed that HSP-70 and XBP-1 loaded heavily on different components, suggesting they capture distinct, non-redundant aspects of the disease's biology and justifying their use in a combined panel [32–38].

The observed reduction in both HSP-70 and XBP-1 levels in patients undergoing chemotherapy provides crucial insight into their potential for treatment monitoring. This decrease likely reflects a direct reduction in tumor burden, as effective chemotherapy eliminates cancer cells, thereby diminishing the primary source of these circulating stress proteins. While some studies have suggested chemotherapy itself can paradoxically increase the release of extracellular HSP-70 from remaining cancer cells, which may promote a pro-tumorigenic microenvironment, our cross-sectional data points to an overall net decrease in the patient group receiving treatment. This suggests that the effect of tumor clearance outweighs the stress-induced release from surviving cells, making these markers a plausible surrogate for therapeutic efficacy [39–48].

Despite these promising results, we must acknowledge the study's limitations. The cross-sectional design, comparing separate groups of patients, provides a snapshot in time but cannot establish causality or track dynamic changes within an individual. Therefore, while our data indicates a difference between treated and untreated states, a longitudinal study that measures these biomarkers in the same patients before, during, and after chemotherapy is essential to validate their utility for monitoring treatment response and predicting recurrence. Furthermore, our cohort was recruited from a single institution, and the sample size is modest. Larger, multi-center studies are required to confirm the generalizability of these findings across diverse populations. Finally, breast cancer is

a heterogeneous disease, and we did not stratify our analysis by molecular subtype (e.g., ER-positive, HER2-positive, triple-negative) or by the specific chemotherapy regimen received, which are important variables that could influence biomarker levels and clinical outcomes. Future work should aim to correlate serum HSP-70 and XBP-1 levels with these clinical parameters to refine their potential role in a precision medicine framework.

In conclusion, serum HSP-70 and XBP-1 are biomarkers associated with breast cancer presence and chemotherapy treatment status. Elevated marker levels at diagnosis fall in response to treatment. Larger, longitudinal studies must validate these findings and determine prognostic value. These biomarkers improve early breast cancer detection and guide personalized patient treatment.

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Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of the Anbar Health Department and the College of Science, Tikrit University, Iraq (Approval No.: TU\COS\BD\F112093). Written informed consent was obtained from all participants prior to enrollment in the study.

Author Contributions

Marwan Sabah Mahdi: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Visualization. Nagham Qasim Kadhim: Supervision, Validation, Writing – Review & Editing, Project Administration. Authors have read and approved the final manuscript.

Data Availability

Data are available from the corresponding author upon reasonable request

Conflict of Interest

Authors declare that there is no conflict

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