

## ORIGINAL RESEARCH

# Clinical diagnostic and prognostic value of plasma Hsp90 $\alpha$ in invasive breast cancer

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**Abstract**

Invasive breast cancer (IBC) is the most common type of breast cancer. This study aimed to determine whether plasma Hsp90 $\alpha$  could be an effective diagnostic and prognostic indicator in IBC patients. The plasma of 545 IBC and 103 non-IBC (NIBC) patients and 189 healthy controls (HC) were collected, and enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of plasma Hsp90 $\alpha$ . The accuracy of Hsp90 $\alpha$ , carcinoembryonic antigen (CEA), and carbohydrate antigen 153 (CA153) for diagnosing IBC were assessed based on the area under the curve (AUC) of the receiver operating characteristic (ROC) curves. Kaplan-Meier and log-rank tests were employed to analyze the association between plasma Hsp90 $\alpha$  levels and progression-free survival (PFS). In the IBC cohort, the plasma levels of Hsp90 $\alpha$  were associated with cancer invasion, TNM (Tumor Node Metastasis) stage, and CEA and CA153 levels, and they were remarkably higher in IBC and NIBC than in control. ROC results revealed the AUC values of Hsp90 $\alpha$  plasma level in IBC and NIBC were 0.877 (95% CI(Confidence Interval): 0.851–0.900,  $p < 0.001$ ) and 0.647 (95% CI: 0.589–0.702,  $p < 0.001$ ). The AUC values of the combination of Hsp90 $\alpha$  with CEA and CA153 in IBC and NIBC were 0.903 (95% CI: 0.880–0.924,  $p < 0.001$ ) and 0.722 (95% CI: 0.667–0.773,  $p < 0.001$ ). Further, patients with high levels ( $>81.4$  ng/mL) of plasma Hsp90 $\alpha$  had a worse PFS than those with low Hsp90 $\alpha$  in IBC. Plasma Hsp90 $\alpha$  levels could be a reliable diagnostic and prognostic marker in IBC. High plasma Hsp90 $\alpha$  levels in IBC was associated with worse PFS.

**Keywords**

Heat shock protein 90 $\alpha$ ; Invasive breast cancer; Diagnostic value; PFS

## 1. Introduction

Breast cancer (BC) is the most common cancer worldwide and the leading cause of cancer-related mortality in women [1]. It is divided into invasive breast cancer (IBC) and non-invasive breast cancer (NIBC). IBC is the main type of BC, mainly consisting of invasive ductal and lobular carcinoma, while NIBC includes ductal and lobular carcinoma *in situ* [2]. In some developed countries, the 5-year relative survival rate of BC patients is above 80% due to early prevention strategies [3].

Although tissue biopsy is the gold standard for accurate diagnosis of BC, it is associated with an increased risk of needle track metastasis. In this regard, blood-based biomarkers represent an alternative non-invasive strategy to improve the efficacy of cancer screening due to their non-invasive nature [4]. However, conventional tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 153 (CA153), have been shown to have low sensitivity and specificity, especially in IBC. Thus, in recent years, there has been a growing demand for discovering novel markers to assist

BC diagnosis and risk stratification due to increasing IBC testing and screening.

Heat shock protein 90 (Hsp90) is an evolutionarily highly conserved intracellular molecular chaperone usually induced in response to cellular stress. Several large-scale studies have shown that the plasma levels of Hsp90 $\alpha$  in multiple tumors were significantly higher than in healthy controls (HC) [5–7]. More importantly, it was reported that the combination of Hsp90 $\alpha$  and alpha-fetoprotein (AFP) significantly improved the diagnostic efficiency for hepatocellular carcinoma (HCC) [8]. In addition, the high Hsp90 $\alpha$  expression in BC tissues and cell lines has also been reported literature [9, 10]. However, whether Hsp90 $\alpha$  can serve as a stable and reliable biomarker in IBC diagnosis and prognosis estimation is yet to be validated.

In this study, we investigated the plasma levels of Hsp90 $\alpha$  in IBC and NIBC, compared with healthy controls, to determine the diagnostic and prognostic significance of plasma Hsp90 $\alpha$  in BC.

## 2. Materials and methods

### 2.1 Patients and samples

The test cohort comprised of 545 IBC, 103 NIBC and 189 HC subjects enrolled from May 2017 to September 2019 at our hospital. IBC and NIBC were diagnosed based on the National Comprehensive Cancer Network (NCCN) guidelines. All patients underwent laboratory examination (including detection of CEA and CA153 serum levels), magnetic resonance imaging and abdominal ultrasound, with their diagnosis confirmed histologically. Written informed consents were obtained from all subjects, and their clinical features were derived from our hospital's electronic records. Tumor stage was determined according to the Tumor-Lymph Nodes-Metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC) staging system [11]. The study exclusion criteria were: (1) presence of >1 malignant tumor in the same period; (2) severe systemic infection, acute or chronic hematologic or autoimmune diseases; (3) blood samples of jaundice cases and patients with hemolysis.

### 2.2 Detection of serum tumor markers

A 4 mL of fasting venous blood was collected in the morning from all subjects with an Ethylenediaminetetraacetic Acid-k2 anticoagulant tube. The plasma levels of Hsp90 $\alpha$  were measured using an ELISA kit (Yantai project Biotechnology Development Co., LTD., Yantai, China). The blood samples were centrifuged at 3000 r/min for 10 min prior to ELISA. The standards were loaded together with the quality controls. Then, 50  $\mu$ L of prepared sample was filled in 96-well plates and supplemented with Hsp90 $\alpha$  HRP-conjugated antibody (50  $\mu$ L). After gently shaking and incubating for 1 h at 37 °C, the plates were washed six times with the provided wash buffer for chromogenic reaction, followed by incubation with peroxide (50  $\mu$ L) and 3,3', 5,5'-tetramethylbenzidine (50  $\mu$ L) for 20 min at 37 °C. Subsequently, the reaction was terminated using an acid stop buffer. Lastly, optical density was detected via a spectrophotometer at 450 nm, with a reference wavelength of 620 nm. The concentration of Hsp90 $\alpha$  protein was determined by the standard curve of optical density values. Serum CEA and CA153 levels were evaluated using electrochemiluminescence immunoassay kits (Cobas, Roche Diagnostics, Munich, Germany) following the manufacturer's instructions. Serum samples were obtained similarly to the plasma samples, except that the blood samples were initially placed in test tubes without anticoagulants and treated as described above.

### 2.3 KM survival analysis takes the best cutoff

For Kaplan-Meier survival analysis, the median value was taken as the cutoff. We used `surv_cutpoint` (Determine the Optimal Cutpoint for Continuous Variables in `survminer`: Drawing Survival Curves using 'ggplot2' (`rdr.io`)) function, data: data frame containing survival data and continuous variables in this work, time, event: column names containing column names time and event data, respectively. Event values were labeled as 0 and 1. Then, we determined the optimal cutpoint

of variables, plotted the cutpoint for Hsp90 $\alpha$ , categorized the variables, and analyzed the obtained survival curves.

### 2.4 Statistical analysis

The SPSS v23 software (International Business Machines Corporation, Armonk, NY, USA) was used for data analysis. Differences between groups were analyzed using the Wilcoxon rank test. Receiver operating characteristic (ROC) curves were established to determine the optimal cutoff thresholds and diagnostic accuracies of continuous variables. *p*-values (all two-sided) less than 0.05 were considered statistically significant. The R v4.03 software was used to plot the Kaplan-Meier curves. All figures were plotted in R language and GraphPad Prism. A two-tailed-sided *p*-value < 0.05 was considered as the threshold for statistical significance.

## 3. Results

### 3.1 Associations between Hsp90 $\alpha$ level and clinical pathological characteristics

A total of 837 cases were included in this study, consisting of 545 IBC and 103 NIBC patients and 189 HC. The median age of each group was 50, 50 and 39 years, respectively, and their clinicopathological characteristics are listed in Table 1. We observed that the plasma level of Hsp90 $\alpha$  was associated with histopathological types, TNM stage and CEA and CA153 levels but not with age and molecular typing (Table 1).

### 3.2 Hsp90 $\alpha$ levels in different groups

The plasma levels of Hsp90 $\alpha$  in the different groups are shown in Fig. 1. They were significantly higher in IBC and NIBC than in HC ( $102.1 \pm 66.01$  ng/mL vs.  $52.48 \pm 10.53$  ng/mL,  $p < 0.001$ ;  $68.52 \pm 31.85$  ng/mL vs.  $52.48 \pm 10.53$  ng/mL,  $p < 0.001$ , respectively), and significantly higher in IBC than in NIBC ( $102.1 \pm 66.01$  ng/mL vs.  $68.52 \pm 31.85$  ng/mL,  $p < 0.001$ ). The plasma levels of Hsp90 $\alpha$  in TNM I–IV stage were  $70.82 \pm 53.89$  ng/mL,  $75.40 \pm 58.49$  ng/mL,  $90.08 \pm 73.15$  ng/mL,  $139.3 \pm 131.4$  ng/mL, indicating an association with increased TNM stage. In pairwise comparisons, the plasma levels of Hsp90 $\alpha$  were significantly higher in stage III and stage IV patients compared with stage I patients ( $p = 0.017$  and  $p < 0.001$ , respectively).

### 3.3 Accuracy of Hsp90 $\alpha$ , CEA and CA153 in diagnosing IBC

ROC curve analysis was conducted to assess the diagnostic efficiency of Hsp90 $\alpha$  with CEA and CA153 in diagnosing IBC and NIBC. The analysis was performed after dividing the patients into an IBC and NIBC cohort. The AUC value of plasma Hsp90 $\alpha$  in the IBC cohort was 0.877 (95% CI: 0.851–0.900, sensitivity: 90.8%, specificity: 72.3%,  $p < 0.001$ ) while the AUC values of CEA and CA153 were 0.625 (95% CI: 0.588–0.660, sensitivity: 42.75%, specificity: 79.79%,  $p < 0.001$ ) and 0.628 (95% CI: 0.592–0.663, sensitivity: 25.5%, specificity: 96.8%,  $p < 0.001$ ), respectively. The AUC value of plasma Hsp90 $\alpha$  in the NIBC cohort was 0.647 (95% CI: 0.589–0.702, sensitivity: 61.5%, specificity: 72.3%), indicat-

**TABLE 1. Demographics and pathological clinical features of the study subjects.**

Variables	Case (N = 648)	Hsp90 $\alpha$ (ng/mL) Mean $\pm$ SD	Hsp90 $\alpha$ (ng/mL) Median (min, max)	<i>P</i>
Age (y)				
<50	331	79.69 $\pm$ 64.72	67.30 (14.58, 401.00)	0.064
$\geq$ 50	317	91.06 $\pm$ 89.59	66.70 (16.00, 668.00)	
Types				
Healthy controls	189	52.48 $\pm$ 10.53	51.60 (14.04, 90.20)	<0.001
Invasion	545	102.10 $\pm$ 66.01	87.09 (50.50, 668.00)	
Non-invasion	103	68.52 $\pm$ 31.85	71.40 (14.58, 140.00)	
TNM				
I + II	408	74.01 $\pm$ 57.10	81.00 (14.58, 363.40)	<0.001
III + IV	240	107.90 $\pm$ 105.3	86.70 (19.87, 668.00)	
ER				
Positive	479	85.24 $\pm$ 75.06	68.00 (14.58, 668.00)	0.805
Negative	169	86.95 $\pm$ 88.92	62.75 (16.00, 565.00)	
PR				
Positive	455	83.30 $\pm$ 71.36	66.85 (18.13, 668.00)	0.238
Negative	193	91.11 $\pm$ 93.62	67.70 (14.58, 565.00)	
HER2				
Positive	147	78.61 $\pm$ 73.48	64.95 (14.58, 565.00)	0.514
Negative	501	83.00 $\pm$ 71.21	67.50 (16.00, 668.00)	
CEA (ng/mL)				
$\leq$ 5	561	79.39 $\pm$ 66.20	65.95 (14.58, 668.00)	<0.001
>5	87	130.50 $\pm$ 129.00	73.85 (16.00, 565.00)	
CA153 (U/mL)				
$\leq$ 31.3	551	79.47 $\pm$ 60.73	66.70 (14.58, 668.00)	<0.001
>31.3	97	108.40 $\pm$ 100.00	72.70 (19.87, 565.00)	

*Hsp90 $\alpha$* , Heat shock protein 90 $\alpha$ ; *SD*, Standard Deviation; *TNM*, Tumor Node Metastasis; *ER*, Estrogen receptor; *PR*, Progesterone receptor; *HER2*, Human Epidermalgrowth Factor Receptor-2; *CEA*, Carcinoembryonic Antigen; *CA153*, Carbohydrate Antigen 153.

ing that the plasma Hsp90 $\alpha$  had a limited diagnosis efficiency in NIBC. These results suggest that Hsp90 $\alpha$  combined with CEA and CA153 had higher diagnostic efficacy and could be a more effective predictor of IBC risk. (Table 2, Fig. 2)

### 3.4 Progression-free survival (PFS) based on the Hsp90 $\alpha$ expression

Kaplan-Meier survival curves are shown in Fig. 3, and the results demonstrated that higher Hsp90 $\alpha$  levels (>81.4 ng/mL) were associated with poorer PFS in IBC patients compared with those with low levels of plasma Hsp90 $\alpha$ .

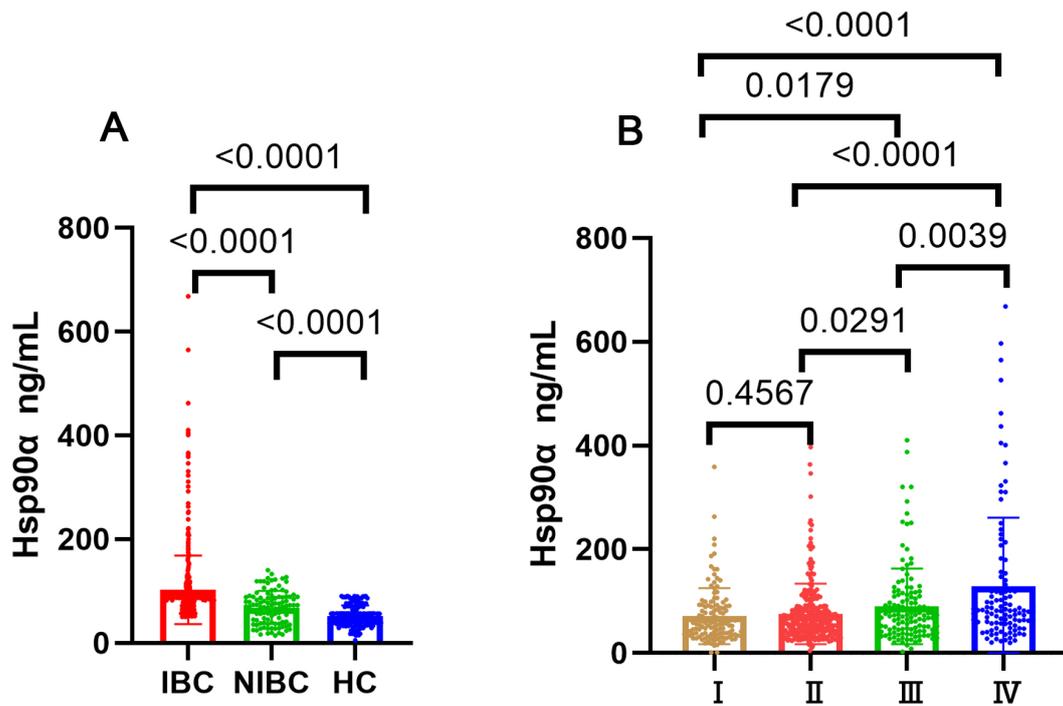
## 4. Discussion

Hsp90 $\alpha$  is an abundant chaperone in the intracellular and extracellular space [5]. Plasma H is a pan-cancer biomarker used in clinics due to its high expression in cancer cells and non-invasive detection by ELISA from routine blood draws [7]. Increasing evidence has recognized Hsp90 $\alpha$  as playing

an important part in modulating the conformation, stability and function of oncogenic proteins involved in cancer cell proliferation, apoptosis, cell cycle, migration and invasion [12–15]. Given the role of Hsp in cancer biology, it has also been suggested as a potential therapeutic target. Most of the Hsp inhibitors used in clinical trials target Hsp90 [16–18].

In this study, we found that plasma Hsp90 $\alpha$  was significantly higher in invasive histological subtypes and increased TNM stage (Fig. 1). However, there was no correlation between the level of plasma Hsp90 $\alpha$  and the molecular subtypes of ER, PR and HER2 (Table 1). Previous studies have shown a statistically significant positive correlation between nuclear Hsp90 and TNM stage via tissue immunostaining, indicating that elevated nuclear Hsp90 could serve as an indicator of BC severity [9]. Thus, the quantitative detection of Hsp90 $\alpha$  levels in peripheral blood plasma samples is clinically more practical than qualitative measurement in tissue samples via immunochemistry.

This study aimed to investigate the diagnostic value of



**FIGURE 1.** Plasma levels of Hsp90 $\alpha$  in (A) different groups (IBC, n = 545; NIBC, n = 103; HC, n = 189), and (B) different TNM stages (I, n = 124; II, n = 284; III, n = 131; IV, n = 109). Hsp90 $\alpha$ , Heat shock protein 90 $\alpha$ ; IBC, Invasive Breast Cancer; NIBC, Non-invasive Breast Cancer; HC, Healthy Controls.

**TABLE 2.** Main parameters of ROC curve analysis results and the pairwise comparison of the ROC curves.

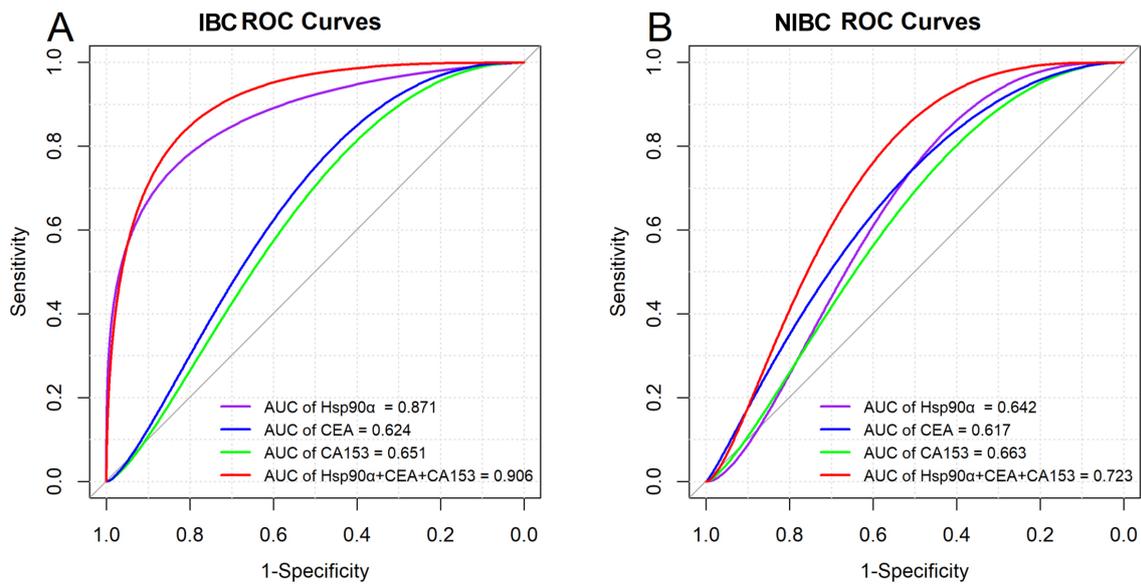
Variables	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	p
<b>IBC-HC</b>						
Hsp90 $\alpha$	0.877	(0.851, 0.900)	57.01	90.80	72.30	<0.001
CEA	0.625	(0.588, 0.660)	2.04	42.75	79.79	<0.001
CA153	0.628	(0.592, 0.663)	21.80	25.50	96.80	<0.001
Hsp90 $\alpha$ + CEA + CA153	0.903	(0.880, 0.924)		90.10	72.90	<0.001
<b>NIBC-HC</b>						
Hsp90 $\alpha$	0.647	(0.589, 0.702)	57.01	61.50	72.30	<0.001
CEA	0.635	(0.577, 0.691)	1.96	51.90	76.10	<0.001
CA153	0.643	(0.585, 0.698)	17.60	36.50	87.20	<0.001
Hsp90 $\alpha$ + CEA + CA153	0.722	(0.667, 0.773)		52.90	85.60	<0.001

AUC, Area Under the Curve; CI, Confidence Interval; CEA, Carcinoembryonic Antigen; Hsp90 $\alpha$ , Heat shock protein 90 $\alpha$ ; CA153, Carbohydrate Antigen 153; IBC-HC, Comparison between IBC group and HC group; NIBC-HC, Comparison between NIBC group and HC group.

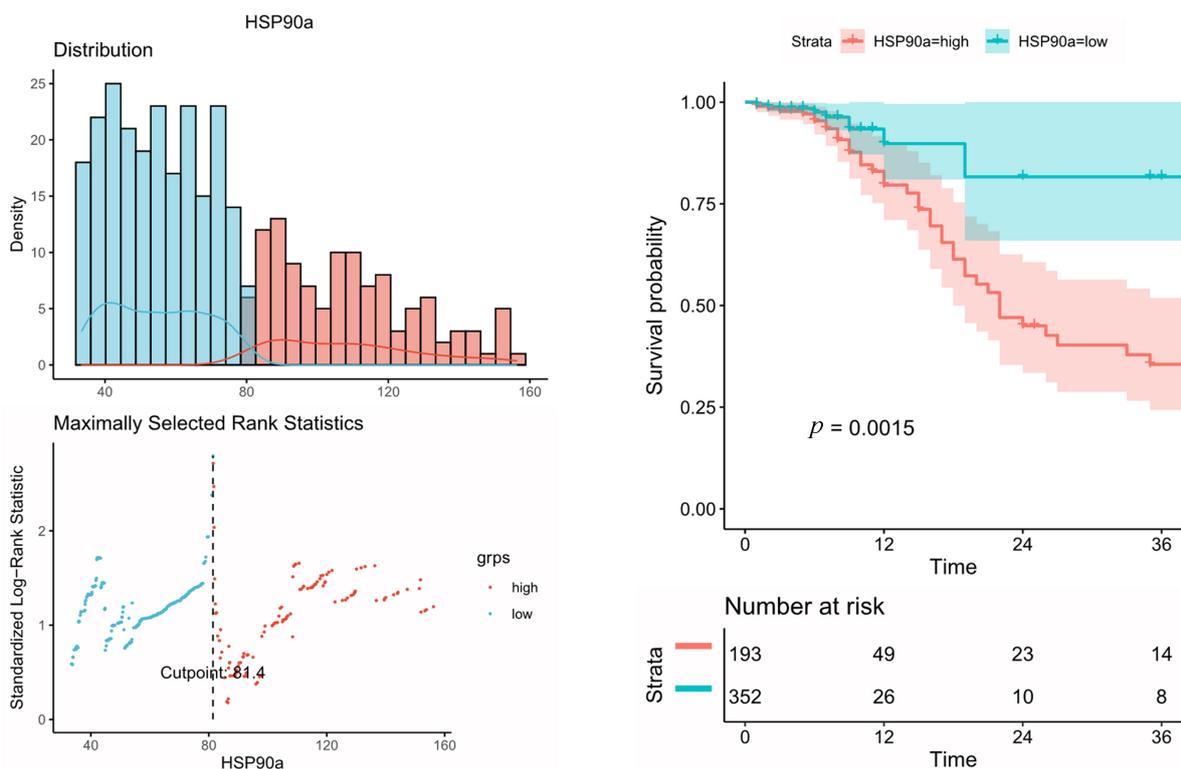
plasma Hsp90 $\alpha$  in BC patients by comparing its level in IBC, NIBC and HC. Our findings showed that the plasma level of Hsp90 $\alpha$  in IBC was significantly higher than in NIBC and HC cohorts and was positively associated with the TNM stage, especially stage IV. Plasma Hsp90 $\alpha$  levels had superior diagnosing performance in IBC compared with CEA and CA153 in breast cancer patients. This finding was consistent with a study showing plasma CEA and CA153 having poor diagnostic accuracy for distinguishing BC from non-BC [19]. Subgroup analysis showed that the plasma levels of Hsp90 $\alpha$  had limited diagnostic efficiency in NIBC. A combination of Hsp90 $\alpha$  with CEA and CA153 significantly improved diagnostic efficiency

compared to single-marker analysis in IBC, but not in NIBC.

Log-rank analysis was performed based on the distribution of Hsp90 $\alpha$  in all clinical patients to evaluate the association between Hsp90 $\alpha$  expression and IBC-specific survival. Cox proportional hazard model suggested an Hsp90 $\alpha$  level of 81.4 ng/mL as the optimal cutoff value. A significant association was observed between Hsp90 $\alpha$  expression and survival in the breast cancer cohort. The predictive function of Hsp90 $\alpha$  showed that patients with high levels (>81.4 ng/mL) of plasma Hsp90 $\alpha$  had a worse outcome than those with low levels of Hsp90 $\alpha$  in IBC. We also found a strong association between high intracellular Hsp90 expression and decreased survival in



**FIGURE 2. ROC curve analysis for diagnosis efficiency of Hsp90 $\alpha$ , CEA and CA153 in (A) IBC and (B) NIBC.** ROC, receiver operating characteristic curve; Hsp90 $\alpha$ , heat shock protein 90 $\alpha$ ; CEA, carcinoembryonic antigen; CA153, carbohydrate antigen 153. ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; IBC, Invasive Breast Cancer; NIBC, Non-invasive Breast Cancer.



**FIGURE 3. Progression-free survival (PFS) of IBC patients based on baseline Hsp90 $\alpha$  expression.** Hsp90 $\alpha$ , heat shock protein 90 $\alpha$ .

primary BC, both among the entire patient cohort and the node-negative subset [20]. Further, in a study by Adeela *et al.* [21], the authors reported that Hsp90 had a higher affinity for Hsp90 inhibitors in cancer cells compared to normal cells, indicating

the tumor selectivity of Hsp90 inhibitors. Therefore, these data suggest that Hsp90 inhibitors in BC could stratify patients based on Hsp90 expression, could be used to develop assays for improving patients' selection for Hsp90 inhibitors and served

as an indicator of therapeutic effectiveness.

## 5. Conclusions

The plasma level of Hsp90 $\alpha$  was statistically different between HC, NIBC and IBC, and was associated with invasion, TNM stage and CEA and CA153 levels in IBC. The combination of Hsp90 $\alpha$ , CEA and CA153 significantly improved the diagnostic efficiency of IBC. Further, high Hsp90 $\alpha$  expression in IBC was associated with worse PFS. Thus, plasma Hsp90 $\alpha$  can be considered a fast, non-invasive and practical indicator that can be used to improve the diagnosis and prognostic efficiency of IBC, with the use of Hsp90 inhibitors demonstrating promising potential in stratifying BC patients based on Hsp90 expression.

## AUTHOR CONTRIBUTIONS

CW and YH designed the research study. YL, SL, ZC and YT performed the research. YH and YL analyzed the data. YH wrote the manuscript. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Guangxi Medical University Tumor Hospital (NO. LW2020052) and was performed following the Declaration of Helsinki and our hospital ethical guidelines.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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