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Correlation between Serum MACC-1 & T Stage and Nodal Status of the Breast Cancer Patients

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Abstract

Breast cancer is the leading cause of cancer-related death among females. The current study is one of the initial studies to evaluate the diagnostic value of novel serum MACC-1 markers in breast cancer patients. Various other serum biomarkers have been used for the diagnosis of breast cancer but this marker proved a good sensitivity and/or specificity. This cross-sectional study included 32 breast cancer patients and 32 normal healthy controls. Study subjects demographic, pathologic, and clinical information were recorded. Random blood samples were collected from the antecubital vein after aseptic precaution with 0.5% chlorhexidine gluconate. About 4.0 ml of venous blood was collected into a red screw-capped tube. Serum MACC-1 was assessed by a double-antibody sandwich ELISA method by using the commercially available kit in the Department of Laboratory Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. In this study, serum MACC-1 levels were significantly elevated ($p< 0.0001$) in breast cancer patients compared to the control group. The mean serum MACC1 was elevated in BC patients (55.21 ± 14.75 pg/ml) compared with healthy controls (38.19 ± 11.42 pg/ml) ($P<0.0001$). The median age was 46.3 years in BC patients and 40.2 ± 8.4 years in the control group ($p <0.0001$). Higher serum MACC1 levels were observed with increasing TNM stages ($p < 0.0001$). Therefore, this study showed that serum MACC-1 can be a potential biomarker for the diagnosis of breast cancer.

Keywords: Serum MACC-1 & T Stage; Breast Cancer; Carcinoembryonic Antigen; Serum Biomarker; Tumor Progression

Abbreviations

MACC-1: Metastasis-Associated in Colon Cancer; TNM: Tumour, Node, Metastasis; BC: Breast Cancer; ELISA: Enzyme-Linked Immunosorbent Assay.

Introduction

Breast cancer is the leading cause of cancer-related death among female [1]. It is the most common cancer type among females worldwide affecting 1 in 8 women [2]. As of 2015, breast cancer is still a leading cancer of women in Bangladesh. It has become a hidden burden which accounts for 69% death of women within the country. The rate grows up day to day due to unawareness of the people, lack of confidence about medical treatment, improper screening, maltreatment, and lack of motivation to go for institutional treatment and management [2]. However, in the developing nations the survival of patients with breast cancer is low, owing to the advanced stage at presentations

[3]. The outcome of the breast cancer patients can be greatly improved by early detection of the disease coupled with effective treatment [4]. There are various biomarkers to screen, diagnose or predict the outcome for breast cancer. Many identified biomarkers such as cancer antigen-19.9 (CA19.9), carcinoembryonic antigen, and cancer antigen 125(CA125), CA 15-3 and CA 27,29 have little clinical value due to low sensitivity, specificity and reproducibility [5]. So, novel biomarkers are urgently needed to detect early stage Breast Cancer [6]. Metastasis associated in colon cancer-1 (MACC-1) is a newly identified tumor marker, first identified in colon cancer tissue as a prognostic indicator and inducer of metastasis [7].

This gene is located on human chromosome 7p21q and regulates hepatocyte growth factor HGF-MNET pathway-a key part in cellular growth, angiogenesis, invasiveness and metastasis [8]. It is also found to express in other normal and cancerous tissue of gastrointestinal tract, pancreas, ovary, breast, pituitary gland, kidney, lung, bone marrow etc [7]. A previous study associated MACC-1 polymorphisms with HER2-positive BC patient suggesting that MACC-1 is a potential BC biomarker [8]. With the aim, this study was conducted to evaluate the serum MACC-1 level as a new diagnostic marker of breast cancer and correlated with TNM staging. This prospective study was conducted from July 2022 to June 2023 at the department of Laboratory Medicine, BSMMU in collaboration with Department of Surgery, BSMMU. We enrolled 64 cases who had their clinical assessment, radiological investigations and biopsy from the tumor. The control subjects were matched with the study group who had no disease at the time of study or in the past. The blood samples of MACC-1 were taken from the study and the control groups before starting any therapy. After separation, the serum samples were stored at -20ºC. The tests were performed by double antibody sandwich ELISA Kit according to the manufacture's protocol [9]. The blood samples were taken properly with safety precautions and ran in the defined machines accordingly specific for them and compared. The parameter used to diagnose breast cancer patients and correlated with TNM staging [10-12].

General Objective: To evaluate the correlation of serum MACC-1 with T stage and Nodal status of the breast cancer patients

Materials and Methods

This study was a cross sectional study. Potential study participants were any adult (≥ 18 years) patients who were histopathologically diagnosed cases of breast cancer Healthy subjects were who had no history of previously diagnosed diseases. Purposive sampling methods were used as per inclusion-exclusion criteria.

Sample size was 64. Inclusion criteria: Age ≥ 18 years. Any adult female (≥ 18 years) patients who were histopathologically diagnosed (According to The Nottingham modification of the Bloom Richardson grading system): cases of breast cancer (stage 0-III) before surgery or chemotherapy. The diagnosis of breast cancer was based on clinical assessment, radiological investigation and biopsy from the tumor. Patients were staged according to the TNM staging system. Healthy subjects were none have previously diagnosed diseases and were physically and mentally fit. Exclusion criteria: Age ≤18 years, did not give written consent, patients who received neo adjuvant chemotherapy before surgery, recurrent breast cancer. Venous blood (4.0 ml) was collected with aseptic precaution. Blood were collected with no anticoagulant for collecting serum in red tubes for MACC-1 level. Tubes were kept standing for 30 minutes. Then blood was centrifuged at 3000 rpm for 5 minutes and supernatant serum was separated into an Eppendorf tube with the help of a micropipette for storage and analysis. Separated serum was stored at -20°C until analysis was done and for further use.

This procedure was done on 5 successive occasions (15 samples per occasion) for measurement of serum MACC-1. Serum MACC-1 were assessed by ELISA method by using the commercially available kit in the Department of Laboratory Medicine. A double-antibody sandwich ELISA was conducted to detect serum MACC-1 according to manufacturer's protocol. Cut-off points of serum MACC-1 level: 38.25pg/ml [13-16].

Results

This study included 32 breast cancer patients and 32 normal healthy controls. Patient median age was 46.3 years and 40.2± 8.4 years in control group ($p = 0.0001$) in this study (Table 1). The mean serum MACC1 was elevated in BC patients (55.21 ± 14.75 pg/mL) compared with healthy controls (38.19 ± 11.42 pg/mL) ($P< 0.0001$, Table 3). Compared with the healthy control, serum MACC1 were elevated in BC patients with increasing (I, II or III) (Table 2). In the study group, serum MACC-1 level increased with the increasing T-stage of the tumor and the difference was statistically significant. Further serum MACC-1 levels were higher in patients with positive axillary lymph nodes compared to those without nodal disease (59.21 ± 14.75 pg/mL, 55.21 ± 14.75 pg/mL, respectively; $p = 0.005$) (Table 4). Higher serum MACC1 levels were also observed with increasing TNM stages ($p < 0.0001$) (Table 4).

Age group (in years)	Group I (n=32) (CA Breast)	Group II (n=32) (Healthy control)	p value
<20 years	02(6.25%)	4(12.5%)	<0.001[s]
21-30 years	16(50.00%)	09(28.12%)	
31-40 years	07(21.87%)	10(31.25)	
41-50years	04(12.5%)	05(15.64)	
51-60 years	02(6.25%)	03(9.37)	
>60 years	01(03.13%)	01(03.12%)	
Mean±SD Range	46.7±10.6 (20-61) years	40.2±8.4 (22-60) years	

Table 1: Age distribution of the study subjects (N=64).

Histopathological grading	Frequency	Percent	p value
Grade I	7	21.87%	<0.001[s]
Grade II	20	62.60%	
Grade III	5	15.62%	
Total	32		

Table 2: Distribution of the study subjects according to histopathological grading in group I (n=32).

Variables	Group I (n=32)	Group II (n=32)	p value
Serum MACC-1 pg/ml	55.21 ± 14.75 pg/ml	38.19 ± 11.42 pg/ml	<0.0001

Table 3: Comparison of the serum MACC-1 value between two group N=64

Variables	Group I (n=32)	Group II (n=32)	p value
SL No.	T stage	Serum MACC-1 (ng/ml) Mean ± SD	p value
Serum MACC-1 pg/ml	55.21 ± 14.75 pg/ml	38.19 ± 11.42 pg/ml	<0.0001
1	T1	55.14 ± 8.14	< 0.001
2	T2	56.80 ± 9.47	
3	T3	58.43 ± 6.25	
4	T4	59.27 ± 11.47	
5	Lymph Node Status		
	LN+	57.36 ± 10.21	0.005
	LN-	52.15± 9.23	

Table 4: Correlation between serum MACC-1 and T stage and Nodal status of the breast cancer.

Discussion

This study is one of the initial studies to evaluate the diagnostic value of novel serum MACC-1 markers in breast cancer patients. Various other markers can be used for the diagnosis of breast cancer but those markers fall short of a good sensitivity and/or specificity. Thus a search for a better serum biomarker remains imperative. This study included 32 breast cancer patients, and 32 normal healthy controls. Patient median age was 46.3 years and 40.2 ± 8.4 years in control group (p <0.0001). A study found the patient's median age was 48.3 years in breast cancer patients and 41.7 years in healthy subjects which were nearly consistent with this study [6]. Ahmed M, et al. [9] in 2000 found in their study that all the patients were females with the mean age of 46.7 ± 10.6 years and 40.2 ± 8.4 years in the control group (p =0.0001) which was also near similar to this study. This study showed most breast cancer patients belong to Grade II which was 68.75% (Table 2). Ahmed M, et al. [9] in 2000 also found maximum number of patients in grade II tumor (61.7%). Current study showed the mean serum MACC-1 was elevated in breast cancer patients (55.21 ± 14.75 pg/

ml) compared with healthy controls (38.19 ±11.42 pg/ml) (p<0.0001, Table 3).

Another study found the mean serum MACC-1 level in breast cancer patients was 3.46 ± 1.3 ng/ml which was significantly higher than control mean serum MACC-1 level (1.90 ±0.2 ng/ml) (p< 0.0001) [10]. Compared with the healthy control, serum MACC-1 was elevated in breast cancer patients of grade (I, II or III) (Table 2).

Higher serum MACC1 levels were also observed with increasing tumor grade (p =0.007) in a different study [9]. This study showed that serum MACC-1 can be a potential biomarker for diagnosis and tumor progression in patients with breast cancer. Our study showed a significant rise in the serum MACC-1 levels with the increasing tumor size, grade and TNM stage (Table 4). Also significantly higher serum MACC-1 levels were noted in our BC patients with positive lymph nodes (Table 4).

Thus, a rising serum MACC-1 level may indicate tumor progression. These similar findings were also noted by Tan W, et al. [6] in their study. Another study showed an increased MACC-1 in tumor tissue and its positive correlation with TNM stage, tumor size and nodal status [10]. This study showed that serum MACC-1 can be a potential biomarker for diagnosis and tumor progression in patients with breast cancer. This study demonstrated that serum MACC1 levels were elevated in Breast Cancer patients compared with control groups and well correlated with TNM staging, suggesting that MACC-1 might act as a useful serum biomarker for distinguishing between early BC patients and healthy control [17-19].

Conclusion

This study showed that serum MACC-1 can be a potential biomarker for diagnosis and tumor progression in patients with breast cancer. Being least invasive and easily detectable, serum MACC-1 can supersede other biomarkers that require tissue sample. Further prospective studies are warranted to validate our findings.

Our study demonstrated that serum MACC1 levels were elevated in BC patients compared with control groups, suggesting that MACC1 might act as a useful serum biomarker for distinguishing between BC patients and healthy controls.

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