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Original Article

Pathology Section

Preoperative Biochemical, Haematological and Radiological Parameters in Breast Cancer: A Case-control Study

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ABSTRACT

Introduction: Haematological, biochemical and radiological investigations are prerequisite for surgical resection in breast cancer. Deranged parameters predict a poorer outcome following surgery and also may adversely influence the risk factors, clinical presentation, predict morbidity, mortality and provide guidelines for treatment in breast cancer.

Aim: To evaluate the significance of breast cancer preoperative investigation when compared with apparently normal control. To assess the association of the significant preoperative investigations with the established breast cancer risk factors, clinical findings and histopathological prognostic factors.

Materials and Methods: This was a case-control retrospective study with 156 histopathologically confirmed breast cancer cases and 102 controls and data were collected through structured questionnaire that included risk factors, clinical, histopathologic, and investigation details. Descriptive statistics, Pearson's chi-square, Odds ratio, Student's t-test and ANOVA were calculated.

Results: There were 3 (1.9%), 81 (51.9%) and 72 (46.2%) cases of Grade I, II and III respectively. When compared to apparently normal controls haemoglobin (Hb), RBC, ESR, RBS, Urea, Creatinine, Sodium, Potassium and Chloride levels were statistically significant. On analysing these significant presurgical investigations with the established breast cancer risk factors, clinical findings and histopathological prognostic factors it was found that Hb with grade; WBC with stage; urea with lymphadenopathy and nipple discharge; creatinine with in-situ and Lymphovascular Invasion (LVI); sodium with grade, mobility of breast lump, lymph node metastasis and Progesterone Receptor (PR); potassium with in-situ had significant association. Radiological parameters were not statistically significant.

Conclusion: The results obtained indicate that the presence of preoperative anaemia, leukocytosis and renal impairment has adverse influence in breast cancer and thereby aid to plan the treatment accordingly.

Keywords: Anaemia, Clinical findings, Investigations, Prognosis, Renal impairment

INTRODUCTION

Carcinogenesis is primarily considered as a genetic disease and influenced by epidemiologic, environmental, demographic and other risk factors. The common presentation of breast cancer is a lump in the breast. On examination, a clinical diagnosis of breast cancer can arrive which is confirmed by gold standard histopathology following surgical resection. Prior to surgery a battery of investigations which includes haematology, biochemistry and radiology are mandatory to assess the risks associated with surgery. The chronic illnesses are known to have a direct impact on blood parameters and other vital organs, so it is necessary to study the changes in haematological, biochemical and radiological parameters in cancer patients. With the advancement in cancer research, a biomarker that can diagnose, predict or monitor several cancers has been established. Breast cancer, the most common malignancy among women has no definitive biomarker. In diabetes when ligands bind to the insulin receptors present on the breast malignant cells, multiple signalling pathways are activated and are capable of stimulating cell proliferation and metastasis [1].

The aetiology of anaemia in breast cancer could be caused by bleeding associated with iron deficiency in ulcerating cancer; nutritional deficiencies due to anorexia; bone marrow damage, bone marrow metastasis suppressing erythropoiesis; haemolysis due to infection in fungating cancer and the malignant process itself. Leukocytes may directly contribute to thrombus formation and disease progression through release of tissue factor, vascular endothelial growth factor, TNF-α, IL-1, and interferons. Preoperative thrombocytosis associated with poor prognosis and survival in bronchial cancer, gastric cancer, gynaecological cancer, oesophageal cancer has been reported [2-4]. It is a common observation that cancer patients are prone to dehydration due to vomiting, diarrhoea or inadequate intake of fluids leading to Renal Impairment (RI). RI also reduce overall survival and increases cancer-related morbidity and mortality.

Analysis of haematological, biochemical and radiological parameters are easy and rapid compared to other biochemical markers which may predict the prognosis of the breast cancer. Although there is published data showing association of some of the preoperative investigation parameters in breast cancer individually, there is no study where association of all the preoperative haematological, biochemical, radiological investigations and extensive clinical parameters with breast cancer analysed under one roof to the best of authors knowledge. In view of above present study was undertaken to evaluate the significance of breast cancer preoperative investigation when compared with apparently normal control and further to assess the association of the significant preoperative investigations with the established breast cancer risk factors, clinical findings and histopathological prognostic factors.

MATERIALS AND METHODS

This case-control retrospective study was conducted at JSS Medical College hospital at Mysuru, India from January 2013 to June 2016. Inclusion criteria for cases were women with histopathologically confirmed primary breast cancer which included modified radical mastectomy and lumpectomy specimens. Exclusion criteria were those breast cancer patients who had received neoadjuvant therapy, inadequate preoperative investigation reports available from the MRD and recurrent breast cancer. Sample size was calculated based on mean (±4 years)

and standard deviation (±14 years) of age according to previous study [5]. The controls were age matched women who underwent routine health check-up in the same hospital without breast carcinoma. The ratio of case to control was kept at 1.5:1. There were 156 breast cancer cases and 102 women as apparently normal controls. The study protocol was in accordance with the ethical standards of the Institutional Ethical Committee and with the Helsinki Declaration of 1975 that was revised in 2000 (JSSMC/IEC/26/1991/2017-18). Patient consent was not required due to the retrospective nature of this study, as the data was collected as part of routine patient care.

The method of collecting data was through structured questionnaire that included demographics, risk factors, clinical, histopathologic and preoperative investigation details. Demographic details included age and marital status. Risk factors included diet, Body Mass Index (BMI), age at menarche and menopause, menstrual cycle regularity, parity, number of children, breastfeeding and sterilisation. Clinical details included duration of breast lump, associated pain, nipple discharge, mobility of breast lump, breast skin changes, side of involvement, lymphadenopathy, family history of breast cancer, blood pressure, co-morbidities and history of any drug intake (separate data for oral contraceptive pills and any other medication). Histopathological parameters included size of tumour, Lymphovascular Invasion (LVI), in-situ component, metastasis to lymph nodes and distant organs, grade (modified Bloom–Richardson–Elston grading system) [6], stage (American Joint Committee on Cancer TNM system) [7], oestrogen and progesterone receptor status (Allred scoring System) [8] and HER2neu reactivity. Pre-operative investigation details included Haemoglobin (Hb), Red Blood Cell (RBC) count, Packed Cell Volume (PCV), White Blood Cell (WBC), Erythrocyte Sedimentation Rate (ESR), Random Blood Sugar (RBS), serum urea, serum creatinine, serum electrolytes, Echocardiography (ECHO) and Ultrasound Imaging of abdomen and pelvis (USG).

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for Social Sciences (SPSS) version 23.0. Descriptive statistical measures like percentage, mean and standard deviation were applied. Inferential statistical tests Pearson's chi-square, student's t-test and analysis of variation were applied. Estimates of odds ratios and accompanying 95% Confidence Interval were calculated. The difference and association were interpreted as statistically significant when 'p' is <0.05.

RESULTS

At the time of diagnosis, the mean±standard deviation of patients' age was 48.3±14.5 years with a range of 27-84 years. There were 3 (1.9%) of Grade I, 81 (51.9%) of Grade II and 72 (46.2%) of Grade III cases. Similarly, there were (2) 1.3% of Stage I, 96 (61.5%) of Stage II and 58 (37.2%) of Stage III cases. On comparing the preoperative investigation results with the apparently normal controls, authors obtained RBS, urea, creatinine, sodium, potassium, chloride, Hb, RBC count and ESR as significant [Table/Fig-1]. Odds ratio were calculated and found that the odds of women with breast carcinoma are 82% less likely to have deranged blood glucose levels than those without breast cancer with the true population effect between 61% and 92% and found statistically significant [Table/Fig-1].

Significant investigation results obtained on comparing with apparently normal controls were statistically analysed for its association with the established risk factors, clinical data and histopathologic parameters of breast cancer. Those parameters with p-value <0.05 are given in [Table/Fig-2,3]. The mean±SD of all investigations according to three tumour grades and the total mean±SD were analysed [Table/Fig-4].

Parameter	Number of cases (Percent)	Number of control (percent)	p-value	Odds ratio	95% confidence interval	
RBS (mg/dL)						
<150	141 (90.4%)	96 (94.1%)	<0.001	0.175	0.079-0.388	Significant
>150	15 (9.6%)	6 (5.9%)				
Haemoglobin (g/dL)						
<12	60 (38.5%)	55 (53.9%)	0.005	0.621	0.370-0.94	Significant
>12	79 (50.6%)	45 (44.1%)				
Not available	17 (10.9%)	2 (2%)				
RBC count (millions/cumm)						
<3.5	150 (96.2%)	77 (75.5%)	<0.001	0.612	0.324-0.936	Significant
3.5-5	6 (3.8%)	25 (24.5%)				
PCV (%)						
<36	83 (53.2%)	48 (47.1%)	0.334	1.279	0.776-2.10	Not Significant
36-46	73 (468%)	54 (52.9%)				
WBC count (thousands/cumm)						
<4000	18 (11.5%)	23 (22.5%)	0.06	1.622	0.937-2.807	Not Significant
4000-11000	118 (75.6%)	67 (65.7%)				
>11000	20 (12.8%)	12 (11.8%)				
Platelet count (lacs/cumm)						
<1.5	14 (9%)	13 (12.7%)	0.338	1.147	0.547-2.405	Not Significant
1.5-4	137 (87.8%)	88 (86.3%)				
>4	5 (3.2%)	1 (1%)				
ESR (mm/hour)						
<20	Nil	54 (52.9%)	0.002	1.718	1.545-1.911	Significant
>20	14 (9%)	25 (24.5%)				
Not available	142 (91%)	23 (22.5%)				
Urea (mg/dL)						
<40	151 (99.4%)	100 (98%)	0.001	0.318	0.165-0.612	Significant
>40	1 (0.6%)	2 (2%)				
Creatinine (mg/dL)						
<1.4	156 (100%)	101 (99%)	<0.001	0.201	0.105-0.383	Significant
>1.4	Nil	1 (1%)				
Sodium (mmol/L)						
<135	116 (76.3%)	98 (96.1%)	<0.001	0.339	0.069-1.672	Not Significant
>147	2 (1.3%)	Nil				
Not available	35 (22.4%)	4 (3.9%)				
Potassium (mmol/L)						
<5	115 (73.7%)	97 (95.1%)	<0.001	0.146	0.018-1.185	Not Significant
>5	6 (3.8%)	1 (1%)				
Not available	35 (22.4%)	4 (3.9%)				
Chloride (mmol/L)						
<105	73 (49.3%)	90 (88.2%)	<0.001	0.146	0.65-0.329	Significant
>105	42 (26.9%)	8 (7.8%)				
Not available	37 (23.7%)	4 (3.9%)				
ECHO						
Normal	12 (7.7%)	13 (12.7%)	0.349	-	-	Not Significant
Abnormal	30 (19.2%)	3 (2.9%)				
Not available	114 (73.1%)	86 (84.3%)				
USG Abdomen						
Normal	26 (16.6%)	13 (12.7%)	0.241	-	-	Not Significant
Abnormal	32 (20.5%)	21 (20.5%)				
Not available	98 (62.8%)	68 (66.6%)				

[Table/Fig-1]: Characteristics of presurgical investigation statistical analysis results between breast cancer cases and apparently normal control.

DISCUSSION

The preoperative investigations in breast cancer were not only required for evaluating patients overall health status but also useful in predicting the prognosis and outcome of the different treatment

Parameters	Lymphadenopathy	Nipple discharge	Mobility of breast lump
Urea	0.02	0.03	
Sodium			0.002

[Table/Fig-2]: Association of significant laboratory investigations with clinical diagnostic parameters in breast cancer.

Parameters	Progesterone receptor	In-situ	LVI	Lymph node metastasis	Stage
Creatinine		0.047	0.02		
Sodium	0.04			0.01	
Potassium		0.004			
Total count					0.035

[Table/Fig-3]: Association of significant laboratory investigations with histopathological prognostic parameters in breast cancer.

Parameters	Grade 1	Grade 2	Grade 3	Mean±SD	p-value
RBS	110.5±13.4	111.2±49.8	136.5±57.3	122.3±63.8	0.234
Urea	22.5±0.7	25.5±9.8	23.4±4.7	24±7.8	0.556
Creatinine	0.8±0.1	0.9±0.1	0.8±0.1	0.8±0.3	0.504
Sodium	141.5±0.7	140.4±2.6	137.6±4.9	139.2±3.8	0.035
Potassium	4.7±0.2	4.2±0.4	4.3±0.5	4.3±0.4	0.403
Chloride	103.5±3.5	105.5±3.3	103±4.7	104.2±4.7	0.093
Haemoglobin	11.3±0.7	10.8±1.6	10±1.2	11.5±1.8	0.025
RBC	-	4.5±0.5	4.1±0.4	3.3±0.9	0.264
ESR	-	70±28	43.7±17.9	52.5±19.5	0.223

[Table/Fig-4]: Association of significant laboratory investigations with tumour grade in breast cancer.

modalities. The immune functions have an important role in fighting against breast cancer that can be detected by analysing various laboratory investigations. In the present study under one umbrella haematological, biochemical and radiological parameters were analysed and found deranged either due to cancer or as a consequence of immune malfunction. Past literature has found diabetes, anaemia, abnormal leukocyte and platelet counts, renal impairment and radiological abnormalities may influence several mechanisms of breast cancer progression and metastasis [9-13].

RBS test was done to screen the patients for diabetes mellitus. In the present study, it was statistically significant when compared to apparently normal control with high RBS level in about one-tenth of the cases. The mean RBS levels increased along with the grades of breast cancer but were not statistically significant [Table/Fig-4]. Results of the present study were similar to Kaplan MA et al., having no statistical difference for grade, ER and PR positivity, HER2-neu overexpression rate, and tumour size between the diabetic and non-diabetic group [14]. Studies have reported about 1.2–1.5 fold greater relative risk for cancers of breast imparted by diabetes [1]. Some of the risk factors such as ageing, obesity, diet, and physical inactivity are shared between diabetes and breast cancer, resulting in positive association between the two [15]. De Bruijn KMJ et al., results indicated that diabetes is a risk factor for breast cancer, and for cancer-specific mortality [9].

The parameters that aid in detecting anaemia such as Hb, RBC count and PCV were significantly reduced in more than 50% of the cases in present study. Similar findings were reported by other authors [16-19]. Hb level decreased significantly along with breast cancer grades and aid in predicting the poor prognosis [Table/Fig-4]. Anaemia did not show significant association with tumour stage was supported by Akinbami A et al., and Rana APS et al., [19,20] The widely accepted mechanism is the release of many cytokines such as TNF-α, interferon-δ, and IL-1, IL-6 during carcinogenesis that induces iron retention by the reticuloendothelial system, gastrointestinal tract, and liver, thereby exerting an inhibitory effect on erythroid precursors [21]. Anaemia was associated with decreased survival, decreased tumour response, delays in therapy, reduced patient compliance, and directly retracts from patient's therapeutic outcomes [22].

About one-tenth of cases had either low or high levels of WBC count with significant association with the tumour stage [Table/Fig-3]. Rana APS et al., have confirmed the present findings [19]. Leukocytosis association with breast cancer stage predicts poor prognosis which was similar to other authors' findings [23,24]. WBC count did not have statistical significance with any risk factors, clinical details and other histopathological parameters of breast cancer or normal controls. One of the previous studies was concurrent [18], with the present results while others are not [16,17,25]. The frequency of tumour related leukocytosis was highest in Grade 3 (8968.4±3881.7) compared with Grade 2 (8321.7±2502.1) and Grade 1 (6565±473.7) but was not statistically significant [Table/Fig-4]. Pre-treatment leukocytosis was recently identified as one of five clinical factors predictive of increased risk for venous thromboembolism in cancer patients [22]. Leukocytosis was secondary to the production of G-CSF by the tumour, and this was an epiphenomenon of the biologic aggressiveness of the tumour [26]. The mechanism of G-CSF up-regulation is through RAS/RAF/MEK pathway activation and MEK inhibitors are targeted as cancer therapeutics [27]. Breast cancer when metastasises to bone marrow either suppress or stimulate lymphohematopoietic cells resulting varying leukocyte count [11]. However, there was no record of metastasis in the present study and hence the cause for leucopenia cannot be explained.

Majority of the present cases had platelet count within normal range, while one-tenth had thrombocytopenia and 3.2% with thrombocytosis which was not significant. Akinbami A et al., opines that depending on the circumstances both thrombocytosis and thrombocytopenia may, therefore, be associated with breast cancer [20].

Renal impairment was detected in the present patients by estimating serum urea, creatinine and electrolytes constituting Renal Function Test (RFT). While RFT was significant compared to control group OR was statistically significant in urea, creatinine and chloride [Table/Fig-1]. In present study association of clinical findings like lymphadenopathy and nipple discharge with urea, similarly, mobility of breast lump with creatinine was unusual findings among all parameters [Table/Fig-2]. Among histopathological prognostic parameters, there was significant unusual association of creatinine with the presence of in-situ component in the area adjacent to breast cancer and LVI; sodium with PR andmetastasis to lymph node; and potassium with the presence of in-situ component in the present study [Table/Fig-3] and the pathogenesis behind it is yet to be explored. Statistical analysis of the present data showed that creatinine was not associated with any clinical parameters, urea was not associated with any histopathological prognostic parameters and chloride was not associated with either of the above. Lung, prostate, pancreatic, liver and renal cancers seem to be associated to the highest frequency of moderate-severe hyponatremia, whilst breast cancer to the lowest [28] In moderate-severe hyponatremia the risk of death increased 4.28 times compared to those with normal-mild hyponatremia [28]. The severity of RI has to be essentially diagnosed before onset of treatment in breast cancer patients, as it helps to adjust the anticancer drug dosage and reduce over-dosage related side-effects.

In the present study, there was significant relationship between tumour grades and the levels of Hb and serum sodium in response to breast cancer cells [Table/Fig-4]. Similarly, as the breast cancer cells gradually losses its differentiation, there is decrease in the levels of blood sugar, RBC count and ESR but were not statistically significant [Table/Fig-4]. Authors establish a temporal association between anaemia, renal impairment and breast cancer progression.

The radiological parameters- ECHO and USG abdomen and pelvis was performed wherever indicated (30-40% of cases and 15-30%

of controls) and was found to be not significant [Table/Fig-1]. ECHO abnormal findings included left ventricular dysfunction, mitral and aortic regurgitation, sclerotic aortic valve, concentric left ventricular hypertrophy, pulmonary hypertension, pericardial effusion, rheumatic heart disease, left atrial dilatation and mitral stenosis. USG abnormal findings included hepatomegaly, cholelithiasis, renal calculus, ovarian cyst, fibroid uterus, hepatic cyst, splenomegaly and incomplete septate uterus. Both ECHO and USG abdomen and pelvis had abnormal findings in majority of the cases which suggests that there is unusual cause and effect relationship between breast cancer progression and cardiac, abdomen and pelvic organ pathology.

The results of the present study, compared with other studies in breast cancer are tabulated in [Table/Fig-5]. It is evident that Hb and RBC were consistently significant among previous and present study with p-value <0.05. The consistent presence of anaemia in all these several studies may suggest that the supply of nutrition is actively involved in breast cancer progression and prognosis [16-18,25]. Further studies to understand the process of anaemia and renal impairment affecting the breast cancer progression and prognosis are recommended.

Parameters	Ali LO [17]	Olufemi AK et al., [16]	Rana APS et al., [19]	Shrivastava S et al., [18]	Khan S et al., [25]	Our study
Hb		0.000		<0.05		0.005
RBC	<0.05	0.000		<0.05	0.001	<0.001
PCV	>0.05		0.54			0.334
WBC	<0.05	0.009	0.002	>0.05	0.005	0.06
Platelet count	<0.05	0.997		>0.05		0.338
ESR	>0.05	0.000			0.005	0.002

[Table/Fig-5]: Presurgical laboratory investigation p-values obtained by correlating with apparently normal controls is compared between our study and other authors in breast cancer.

LIMITATION

First some of the routinely performed presurgical haematological parameters were not included. Second the reason for association between RFT, clinical and histopathological findings could not be established. Third a limited number of cases with radiological parameters were analysed.

CONCLUSION

In light of the present preliminary study on standard, simple, rapid, minimally invasive preoperative investigations, authors conclude that there was a significant association between anaemia, diabetes, renal impairment and breast cancer when compared to apparently normal controls. Further anaemia, leukocytosis and renal impairment were significantly associated with various clinical findings and histopathological prognostic factors but none with the risk factors in breast cancer. It was evident that the association of anaemia, which was major supply of nutrition, was actively involved in breast cancer progression and prognosis. The results of the present study aid the treating oncologist to plan the treatment accordingly. It is recommended that the pathogenesis of anaemia, leukocytosis and renal impairment in breast cancer progression and prognosis to be explored.

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