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Original Research Article

Retrospective Study of Survival and Clinico Pathological Characteristics of Different Histopathological Grades of Newly Diagnosed Breast Cancer Patients: A Rural Cancer Centre Experience

Anindya Sarkar[1], Soumita Poddar[2], Prem Nath Dutta[3]

[1]Assistant Professor, MD, Department of Radiotherapy, Murshidabad Medical College Hospital, Berhampore, Murshidabad, West Bengal, India – 742101

[2]Associate Professor, MD, Department of Radiotherapy, Murshidabad Medical College Hospital, Berhampore, Murshidabad, West Bengal, India – 742101

[3]Assistant Professor, MD, Department of Radiotherapy & Oncology, Jalpaiguri Government Medical College Hospital, Jalpaiguri, West Bengal, India - 735101

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Corresponding Author: Dr. Anindya Sarkar

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Abstract

Background: Histopathological grading is an essential prognostic tool in breast cancer management. In rural India, limited healthcare access often leads to late diagnosis and poor survival. Understanding the clinico-pathological profile of various tumor grades can help to optimize treatment strategies in resource-constrained settings.

Aim: To evaluate the clinico-pathological characteristics and survival outcomes associated with different histological grades of newly diagnosed breast cancer patients in a rural cancer centre.

Methods: A retrospective observational study was conducted on 486 patients diagnosed with breast cancer between June 2021 and June 2023. Tumors were graded using the Nottingham system. Demographic, pathological, and treatment details were analyzed. Survival outcomes—disease-free survival (DFS) and overall survival (OS)—were assessed using Kaplan-Meier analysis, and associations were evaluated using Chi-square and log-rank tests.

Results: Of the 486 patients, 21.0% had Grade I, 45.7% Grade II, and 33.3% Grade III tumors. Higher tumor grade was significantly associated with larger size, lymph node positivity, HER2 positivity, and triple-negative phenotype ($p<0.001$). Hormone receptor positivity declined with increasing grade. Grade I tumors had superior 3-year DFS (89.2%) and OS (93.1%) compared to Grade III (58.1% and 71.6%, respectively) ($p<0.001$). BMI was also correlated with grade and survival—obese patients (≥30 kg/m²) had a higher proportion of Grade III tumors and poorer outcomes.

Conclusion: Histological grade is a strong predictor of aggressive tumor biology and poor prognosis in breast cancer. In rural settings, early diagnosis and grading-based risk stratification can guide effective treatment planning. Improving access to diagnostic tools and targeted therapies is vital to reducing rural-urban disparities in breast cancer outcomes.

Keywords: Breast cancer, Histological grade, Rural healthcare, Survival analysis, Hormone receptor, Triple-negative, Nottingham grading, BMI.

Introduction

Breast cancer is the most frequently diagnosed malignancy and a leading cause of cancer related death among women worldwide, accounting for approximately 24.5% of all new cancer cases and 15.5% of cancer deaths globally [1]. In India, breast cancer has surpassed cervical cancer to become the most common malignancy in females, with rising incidence and an increasing burden on healthcare, particularly in rural areas [2,3]. Histopathological grading serves as a vital prognostic indicator in breast cancer. The Nottingham Histologic Grade (also known as the Elston–Ellis modification of the Scarff–Bloom–Richardson grading system) remains one of the most widely accepted methods for assessing tumor differentiation [4]. It evaluates three morphological features—tubule formation, nuclear pleomorphism, and mitotic count—to assign tumors as Grade I (well-differentiated), Grade II (moderately differentiated), or Grade III (poorly differentiated) [5]. Higher histologic grades are associated with poor differentiation, higher proliferative activity, and worse prognosis [6].

Numerous studies have demonstrated that high-grade tumors are significantly correlated with adverse clinico-pathological features such as larger tumor size, lymph node positivity, hormone receptor (ER/PR) negativity, HER2 overexpression, and triple-negative phenotype [7,8]. These aggressive biological behaviors contribute to shorter disease-free survival (DFS) and overall survival (OS) [9].

While urban cancer centers in India often have access to advanced diagnostic and therapeutic resources, patients in rural areas face significant barriers including delayed diagnosis, lack of screening programs, inadequate infrastructure, and socioeconomic constraints [10,11]. These disparities directly impact treatment outcomes and survival. Another emerging prognostic factor is Body Mass Index (BMI). Obesity has been linked to more aggressive tumor biology, poorer response to treatment, and reduced survival in breast cancer patients [12]. The mechanism involves chronic inflammation, altered hormone levels, and insulin resistance, which can stimulate tumor growth and progression [13].

Despite the clinical relevance of histological grading and BMI, limited data exist from rural Indian populations. Understanding these correlations in resource-limited settings is crucial for developing region-specific treatment protocols and improving outcomes.

This study aims to evaluate the clinico-pathological characteristics and survival outcomes associated with different histological grades of newly diagnosed breast cancer patients in a rural cancer centre. It also explores the association of BMI with tumor grade and survival, providing insight into its utility as a supplementary prognostic factor.

Materials and Methods

Study Design and Setting: This was a retrospective observational study conducted at a rural cancer centre in India. The study aimed to analyse the survival outcomes and clinico-pathological characteristics associated with different histopathological grades of newly diagnosed breast cancer patients. The data were collected from medical records over a period of two years, from June 2021 to June 2023.

Study Population: A total of 486 newly diagnosed breast cancer patients were included in the study. Patients were categorized into two groups:

- **Metastatic breast cancer (MBC)** patients: *n = 90*
- **Non-metastatic breast cancer (NMBC)** patients: *n = 396*

Inclusion criteria were

- Histologically confirmed diagnosis of primary breast cancer.
- Patients who received their initial diagnosis and treatment at the rural cancer centre during the study period.
- Availability of complete clinical, pathological, and follow-up data.

Exclusion criteria included

- Recurrent breast cancer cases.
- Incomplete records or loss to follow-up immediately after diagnosis.

Data Collection: Data were obtained retrospectively from patient case files, histopathology reports, and hospital databases. The following variables were recorded:

- **Demographic details**: Age, residence, menopausal status.
- **Clinico-pathological parameters**: Tumor size (T-stage), lymph node status (N-stage), metastasis (M-stage), histological type, histological grade (I, II, III), hormonal receptor status (ER, PR), HER2 status, Ki-67 index.
- **Treatment details**: Type of surgery, chemotherapy, radiotherapy, targeted therapy, and hormonal therapy.
- **Survival outcomes**: Disease-Free Survival (DFS) and Overall Survival (OS).
- **Body Mass Index (BMI):** Classified as <18.5 (underweight), 18.5–24.9 (normal), 25–29.9 (overweight), and ≥30 kg/m² (obese).

Definitions

- **Histopathological grade** was assigned based on the Nottingham grading system.
- **Disease-Free Survival (DFS)** was defined as the time from primary treatment completion to the date of recurrence or last follow-up without recurrence.
- **Overall Survival (OS)** was defined as the time from the date of diagnosis to the date of death or last follow-up.

Statistical Analysis: All statistical analyses were performed using SPSS version 21.1. Descriptive statistics were used to summarize demographic and clinico-pathological characteristics. Survival analysis was conducted using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test. Associations between histological grade and clinicopathological features were analyzed using the Chi-square or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee of the cancer centre. As it was a retrospective study, the need for informed consent was waived. Patient confidentiality was maintained throughout the study.

Results

Table 1: Demographic Characteristics of Breast Cancer Patients (n = 486)

Variable	Category	Frequency (n)	Percentage (%)
Age Group (years)	<40	74	15.20%
	40–49	148	30.50%
	50–59	162	33.30%
	≥60	102	21.00%
Menopausal Status	Premenopausal	208	42.80%
	Postmenopausal	278	57.20%
Residence	Rural	396	81.50%
	Urban	90	18.50%

Table 2: Distribution of Patients by Metastatic Status

Group	Number of Patients (n)	Percentage (%)
Metastatic Breast Cancer (MBC)	90	18.50%
Non-Metastatic Breast Cancer (NMBC)	396	81.50%
Total	486	100%

Table 3: Histopathological Grades of Tumors (n = 486)

Grade	Number of Patients (n)	Percentage (%)
Grade I (Well differentiated)	102	21.00%
Grade II (Moderately differentiated)	222	45.70%
Grade III (Poorly differentiated)	162	33.30%
Total	486	100%

Table 4: Clinico-Pathological Features by Histological Grade

Variable	Grade I (n=102)	Grade II (n=222)	Grade III (n=162)	p-value
Tumor Size >2 cm	36 (35.3%)	128 (57.6%)	122 (75.3%)	<0.001
Lymph Node Positive	28 (27.5%)	104 (46.8%)	118 (72.8%)	<0.001
ER Positive	88 (86.3%)	166 (74.7%)	96 (59.3%)	<0.001
PR Positive	76 (74.5%)	154 (69.4%)	78 (48.1%)	<0.001
HER2 Positive	14 (13.7%)	58 (26.1%)	66 (40.7%)	<0.001
Triple Negative	6 (5.9%)	28 (12.6%)	54 (33.3%)	<0.001

Table 5: Treatment Modalities Received by Patients (n = 486)

Treatment Type	Number of Patients (n)	Percentage (%)
Surgery	398	81.90%
Chemotherapy	462	95.10%
Radiotherapy	376	77.40%
Hormonal Therapy	298	61.30%
Targeted Therapy Trastuzumab)	96	19.80%

Table 6: Survival Analysis by Histological Grade

Grade	Mean DFS (months)	Mean OS (months)	3-Year DFS (%)	3-Year OS (%)
Grade I	32.8 ± 4.2	34.5 ± 3.8	89.20%	93.10%
Grade II	30.4 ± 5.6	32.6 ± 5.2	79.60%	86.40%
Grade III	24.1 ± 7.3	26.8 ± 6.7	58.10%	71.60%
p-value	<0.001	<0.001	<0.001	<0.001

Table 7: Relationship between BMI, Histological Grade, and Survival Outcomes (n = 486)

BMI Category (kg/m²)	Grade I (n=102)	Grade II (n=222)	Grade III (n=162)	p-value	Mean DFS (months)	Mean OS (months)	3-Year DFS (%)	3-Year OS (%)
<18.5 (Underweight)	8 (7.8%)	10 (4.5%)	6 (3.7%)	0.21	30.6 ± 5.3	32.4 ± 4.9	82.60 %	85.40 %
18.5–24.9 (Normal)	52 (51.0%)	98 (44.1%)	48 (29.6%)	0.002	31.8 ± 4.6	33.7 ± 4.1	86.90 %	90.10 %
25.0–29.9 (Overweight)	30 (29.4%)	76 (34.2%)	58 (35.8%)		28.4 ± 6.1	30.3 ± 5.8	73.30 %	80.20 %
≥30.0 (Obese)	12 (11.8%)	38 (17.1%)	50 (30.9%)	<0.001	23.9 ± 6.9	26.1 ± 6.3	59.10 %	70.60 %

Table 8: Kaplan-Meier Survival Analysis Summary

Variable	Log-Rank p-value
Histological Grade	<0.001
Hormone Receptor Status	<0.01
HER2 Status	<0.05
Metastatic Status	<0.001

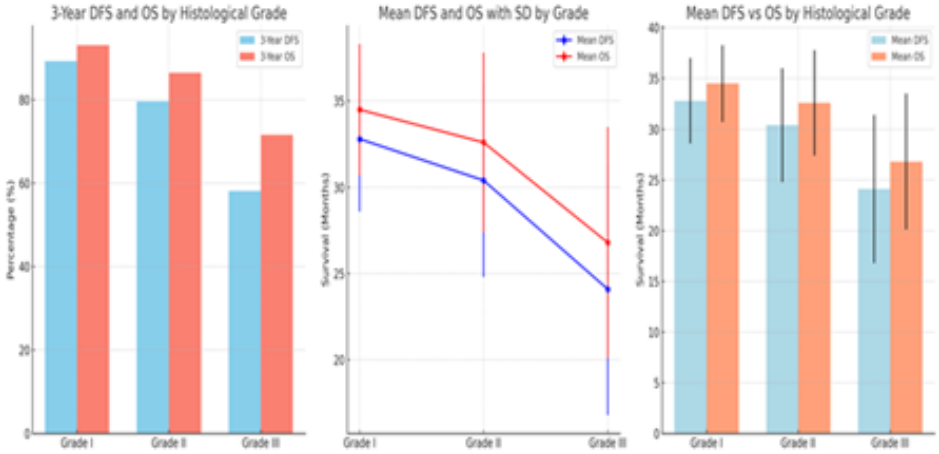

Figure 1: Survival Analysis by Histological Grade

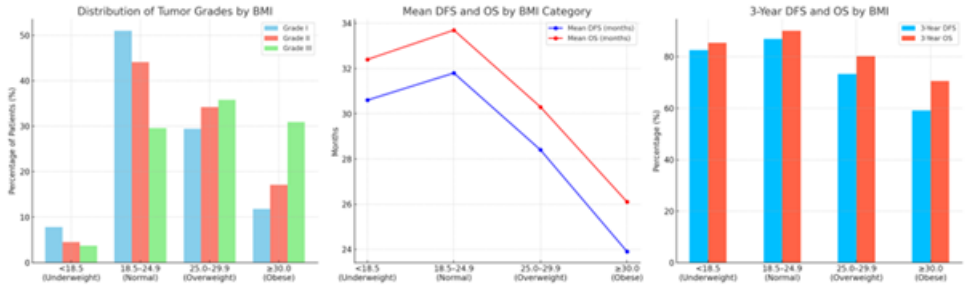

Figure 2: Relationship between BMI, Histological Grade, and Survival Outcomes (n = 486)

In our study population, the majority of participants were between 50 and 59 years of age, accounting for 33.3% (n = 162), followed by those aged 40–49 years at 30.5% (n = 148). Participants under 40 years constituted 15.2% (n = 74), while those aged 60 years and above made up 21.0% (n = 102). Regarding menopausal status, 57.2% (n = 278) of the participants were postmenopausal, whereas 42.8% (n = 208) were premenopausal. The majority of the study population resided in rural areas, representing 81.5% (n = 396), while 18.5% (n = 90) lived in urban areas.

Among the study participants, 396 patients (81.5%) were diagnosed with non-metastatic breast cancer (NMBC), while 90 patients (18.5%) had metastatic breast cancer (MBC), making up the total study population of 486 participants.

In the study population, the majority of patients had moderately differentiated tumors (Grade II),

accounting for 45.7% (n = 222). Well-differentiated tumors (Grade I) were observed in 21.0% of patients (n = 102), while poorly differentiated tumors (Grade III) were present in 33.3% of patients (n = 162). In the study, significant differences were observed across the tumor grades in various clinical characteristics. The percentage of patients with tumors larger than 2 cm increased from 35.3% in Grade I to 57.6% in Grade II, and 75.3% in Grade III ($p < 0.001$). Lymph node positivity was also higher in Grade III (72.8%) compared to Grade II (46.8%) and Grade I (27.5%), with a significant difference ($p < 0.001$). The proportion of estrogen receptor (ER)-positive patients decreased from 86.3% in Grade I to 74.7% in Grade II, and 59.3% in Grade III ($p < 0.001$). Similar trends were seen with progesterone receptor (PR)-positivity, with 74.5% in Grade I, 69.4% in Grade II, and 48.1% in Grade III ($p < 0.001$). HER2 positivity was notably higher in Grade III (40.7%) compared to Grade II (26.1%) and Grade I (13.7%) ($p < 0.001$). The proportion of triple-negative breast cancer patients significantly increased from 5.9% in Grade I to 12.6% in Grade II and 33.3% in Grade III ($p < 0.001$).

In the study, the most common treatment modality was chemotherapy, administered to 95.1% (n = 462) of patients. Surgery was performed in 81.9% (n = 398) of patients, while radiotherapy was given to 77.4% (n = 376) of participants. Hormonal therapy was used in 61.3% (n = 298) of patients. Targeted therapy, specifically trastuzumab, was administered to 19.8% (n = 96) of the patients.

In terms of survival outcomes, significant differences were observed across tumor grades. The mean disease-free survival (DFS) was highest for Grade I at 32.8 ± 4.2 months, followed by Grade II at 30.4 ± 5.6 months, and Grade III at 24.1 ± 7.3 months ($p < 0.001$). Similarly, the mean overall survival (OS) was significantly better in Grade I (34.5 ± 3.8 months), compared to Grade II (32.6 ± 5.2 months) and Grade III (26.8 ± 6.7 months) ($p < 0.001$). The 3-year DFS was 89.2% for Grade I, 79.6% for Grade II, and 58.1% for Grade III ($p < 0.001$), while the 3-year OS was 93.1% for Grade I, 86.4% for Grade II, and 71.6% for Grade III ($p < 0.001$).

In our study, a significant association was found between body mass index (BMI) category and both disease-free survival (DFS) and overall survival (OS) across tumor grades. For patients with a BMI in the normal range (18.5–24.9 kg/m²), Grade I patients had the highest mean DFS (31.8 ± 4.6 months) and OS (33.7 ± 4.1 months), with 3-year DFS at 86.9% and 3-year OS at 90.1%. In comparison, Grade III patients in the same BMI category had a lower mean DFS (28.4 ± 6.1 months) and OS (30.3 ± 5.8 months), with 3-year DFS at 73.3% and 3-year OS at 80.2%. BMI categories under 18.5 (underweight) and 25.0–29.9 (overweight) showed progressively worse outcomes, with 3-year DFS and OS decreasing as BMI increased. Particularly in the obese category (BMI ≥30.0 kg/m²), Grade III patients experienced the lowest mean DFS (23.9 ± 6.9 months) and OS (26.1 ± 6.3 months), with 3-year DFS at 59.1% and 3-year OS at 70.6% ($p < 0.001$).

The survival analysis in our study revealed significant differences in survival outcomes based on several variables. The log-rank test showed that histological grade ($p < 0.001$), hormone receptor status ($p < 0.01$), HER2 status ($p < 0.05$), and metastatic status ($p < 0.001$).

Discussion

In this retrospective study involving 486 newly diagnosed breast cancer patients at a rural cancer center in India, we examined the clinico-pathological characteristics and survival outcomes in relation to histological grade and BMI. Our findings affirm the prognostic relevance of tumor grade and underscore BMI as a potential modifiable factor influencing breast cancer aggressiveness and prognosis. The distribution of histological grades in our cohort—Grade I (21.0%), Grade II (45.7%), and Grade III (33.3%)—is consistent with previous Indian studies, which also report a predominance of Grade II tumors [11,14]. Higher-grade tumors were significantly associated with adverse features, including larger tumor size, increased lymph node positivity, HER2 positivity, and a triple-negative phenotype. These observations align with earlier findings that poorly differentiated tumors exhibit higher proliferative activity and invasive potential [5,6,7]. Estrogen receptor (ER) and progesterone receptor (PR) positivity showed a marked decline with increasing grade—ER positivity dropped from 86.3% in Grade I to 59.3% in Grade III. Similar trends have been reported in global studies and support the view that lower-grade tumors tend to have more favorable hormone receptor profiles, making them more amenable to endocrine therapy [17,18].Triple-negative breast cancer (TNBC), a clinically aggressive subtype lacking ER, PR, and HER2 expression, was significantly more common in Grade III tumors (33.3%) compared to only 5.9% in Grade I. TNBC is widely recognized for its poor prognosis and limited treatment options, particularly in rural or resource-limited settings [15,16]. Survival analysis revealed a strong inverse relationship between histological grade and outcomes. Grade I tumors demonstrated the best 3-year disease-free survival (DFS: 89.2%) and overall survival (OS: 93.1%), while Grade III tumors had significantly lower DFS (58.1%) and OS (71.6%) ($p<0.001$). These results are in accordance with multiple large-scale studies highlighting histological grade as a robust prognostic marker [4,6,9]. A novel aspect of our study is the evaluation of BMI in relation to

tumor grade and survival. Obesity (BMI ≥30 kg/m²) was significantly associated with higher tumor grade and poorer survival outcomes—Grade III tumors accounted for 30.9% of obese patients, with corresponding declines in DFS (59.1%) and OS (70.6%). This supports existing literature suggesting that obesity promotes tumor progression through chronic inflammation, altered adipokine profiles, insulin resistance, and increased estrogen synthesis from adipose tissue [12,13,19]. Furthermore, underweight and overweight patients also showed suboptimal outcomes compared to those with normal BMI, indicating a U-shaped relationship between BMI and prognosis. This finding suggests the importance of maintaining a healthy BMI to potentially improve breast cancer outcomes, a consideration particularly relevant in rural populations where dietary habits and access to care may influence body weight. Treatment modality analysis revealed that patients with Grade I tumors were more likely to receive hormonal therapy, while those with higher-grade tumors were treated more aggressively with chemotherapy.

Trastuzumab use was limited (19.8%), reflecting both HER2-positivity rates and likely restricted access to targeted therapies in rural settings. These treatment disparities could also contribute to differences in survival between grades. Importantly, this study highlights the challenges in rural cancer management. Late presentation, lack of awareness, and limited access to pathology services can delay diagnosis and grading, thereby impacting treatment decisions and prognosis [10,11].

Integrating tumor grading with BMI assessment in routine evaluation could enhance risk stratification and aid in tailoring treatment plans even in resource-constrained settings.

Conclusion

Histological grade is a key prognostic factor in breast cancer, strongly associated with tumor aggressiveness and survival outcomes. Higher grades correlate with larger tumors, lymph node involvement, triple-negative phenotype, and poorer prognosis.

Additionally, elevated BMI, particularly obesity, is linked to higher-grade tumors and reduced survival. In rural settings, early histological grading and BMI assessment can guide effective, personalized treatment. Integrating these low-cost markers into routine practice may improve outcomes and reduce disparities in breast cancer care.

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