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Relevance of Estrogen and Progesterone Receptors in Determining Breast Cancer Prognosis

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Abstract

The Estrogen Receptors (ER) and Progesterone Receptors (PGR) affect Breast Cancer Prognosis (BCP). Breast cancer (BC) cells include ER and PGR. Hormone receptor-positive breast tumors have either progesterone PR-positive (PRP) either ER-positive (ERP). In this study, the ER and PGR and the Nuclear Grade (NG) and Histologic Grade (HG) of the patient's tumor were correlated with the Distant Disease Free Survival (DDFS), Disease Free Survival (DFS), and survival (S) of 1,155 histological Node Negative (NN) BC patients. All patients had surgery without receiving systemic adjuvant treatment. Patients with ERP tumors had considerably better DDFS, DFS, and S than patients with ERN tumors (P =0.004, 0.003, 0.002), but the differences were only marginally different after five years of follow-up. The contrast of such size is inadequate to distinguish between individuals requiring systemic treatment and patients not performing. Like ERP, PGRP tumors had better outcomes, although only in S was the distinction statistically considerable. PGR had no independent impact on the outcome prediction while paired with ER. According to regression analysis, NG represented the most significant single outcome marker. Women with unknown levels of ER, either PGR, had prognoses equivalent to ERP or PGRP malignancies. Given that a more substantial percentage of tumors with unidentified receptors were less than 1.1 cm, there was inadequate tissue for investigation, and the result seemed to be connected to Tumor Size (TS). According to our research, tumor ER is not as good a predictor of prognosis in NN BC patients as NG is, while PGR is either of little or no use. Deciding the type of systemic medicine to provide to these individuals, tumor NG may also be necessary.

Keywords: Estrogen Receptors (ER), Progesterone Receptors (PGR), Nuclear Grade (NG), Histologic Grade (HG), Breast Cancer (BC), Patients.

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1. Introduction

Worldwide, two million women get a breast cancer diagnosis every year. Approximately 70% of breast cancers are ERP and PGRP, and 85% of these tumors affect women over 70. Assessing the probable outcomes and potential course of the illness requires knowledge of the BC prognosis. It refers to the forecasting or assessment of the possible system and survival rates for patients diagnosed with BC. The prognosis is primarily influenced by several variables, including the cancer's stage, the tumor features, the patient's age, general health, and specific biomarkers. Healthcare providers can better adjust treatment regimens and provide patients with helpful information about the course of their condition ought to have an accurate prognosis [1]. The College of American Pathologists (CAP) and the American Society of Clinical Oncology (ASCO) jointly published the ER and PGR.

The PGR testing guidelines aim to increase the analytical performance, diagnostic precision, and therapeutic usefulness of ER and PGR testing as biomarkers for treating women with initial BC. One of the main factors affecting prognosis is the stage of the BC. Stage 0 or stage 1 BC often has a favorable prognosis, with a better likelihood of effective therapy and long-term survival. A more difficult prediction is usually indicated by more advanced stages of BC, such as stage 3 or stage 4, since the disease may have spread to surrounding lymph nodes and distant organs [2]. The most common disease is diagnosed globally in BC. More than seventy percent of all BCs are classified as ERP based on the discovery of ER expression by immunohistochemical in a minimum of 1% of the cells in

the tumor. ER-positive BC has receptors on the cancer cells capable of binding to the estrogen hormone. The response to estrogen might differ from person to person since these tumors have patient-specific hormone sensitivity. While estrogen is essential for forming ERP tumors, the appearance of PR also substantially impacts cells' behavior. PR is an additional marker and increases the tumor's general hormonal sensitivity [3]. The most frequent cancer in women and the second most common disease in BC. BC, ER, and PR positive are a subtype of BC characterized by these receptors on the surface of cancer cells. The growth and development of hormone-sensitive BC depend heavily on these receptors. Estrogen and progesterone are essential for the development and survival of cancer cells. These hormones' binding to the corresponding receptors results in a series of signals that encourage the growth of tumors. As a result, focusing on these receptors has emerged as a critical component of treating breast cancer that is positive for the hormone receptor [4].

During the last 20 years, the mortality rate from BC has significantly decreased. This development may be due to the implementation of cutting-edge management routes, from early diagnosis through therapy. BC continues to be the primary cause of mortality from cancer in women globally. Because of this, predicting BC survival is a complex undertaking that might greatly benefit from creating customized predictive models. In light of this, modern oncology has seen a rise in interest in digital technologies that, to the analysis of large-scale healthcare data, has given rise to new expectations for customized therapy [5]. The development of modern technology has improved the measurements of tailored treatment plans for many illnesses and given light to several diagnostic characteristics. Scientific advances have led to the identification of new treatment targets tailored to various sick situations and the development of numerous gene expression profiles that have enhanced the diagnosis and prognosis of many disease stages. Gene expression profiling also entails deciphering the mRNA signatures in a cell population to distinguish between distinct subgroups of the illness. One of the grave problems for women's health across the world is BC [6]. The purpose of this study is to determine PR and ER affect BCP. ER and PR are known to be present in BC cells. PRP and ERP receptors are present in hormone receptor-positive BC.

The study [7] investigated new prognostic markers for patients with ERP BC tumors utilizing gene copy data to determine if these factors had prognostic significance in subgroups divided by PR. In the current investigation, public data were used, including whole genome gene copy information from 199 patients with ERP malignancies that were not receiving systemic therapy**.** The findings of the current investigation showed that in patients with an ERP /PR tumor have not received systemic treatment, Ras-related protein Rab‑6C (RAB6C) functions as a separate prognostic indicator of the probability of distant recurrence. The paper [8] demonstrated the predictive significance of Ki-67 in patients with early BC that expresses the PGR but lacks the human epidermal growth factor receptor 2 (HER2). Patients with nonmetastatic invasive BC receiving surgery at a single facility between 2009 and 2012 had their records examined. The Overall survival (OS) was the secondary end target, and recurrence-free survival (RFS) was the primary endpoint. Only in cases of early BC with low PGR expression did ki-67 have significance as a prognostic marker. While utilizing Ki-67 to assess the prognosis of BC patients, PGR should be considered.

The study [9] evaluated the role of PGR development in luminal BC, particularly emphasizing the meaning of benefits and its prognostic significance in contrast to Ki67 expression. There was a significant percentage of BC that was ERP/HER2-negative. PGR was biologically stained on full face slices and core needle biopsies (CNB) in order to establish the optimal score cutoff. Although other cutoffs showed predictive relevance, 10% was the optimum cutoff to segregate PGR development into two clinically distinct prognosis groups on CNB. A substantial correlation between aggressive tumor behavior characteristics and poor prognosis was shown by PR negativity. The clinic pathological characteristics of BC that were ERP and PGR -negative (PGR -), as well as to ascertain PGR negativity affected ERP illness. A single institution's consecutive female patients with BC and ERP were included. Binary logistic regression was used to analyze factors related to PGR - illness. With the use of Kaplan-Meier and Cox regression analysis, the oncological outcome was evaluated. PGR- tumors have more aggressive clinicopathological characteristics and poorer oncological outcomes in ERP illness. Depending on the PGR status, neoadjuvant and adjuvant therapy approaches should be customized [10].

The paper [11] assessed tumor PGR mutation prevalence and prognostic relevance in patients with estrogen receptor ERP metastatic BC. In the retrospective research that received IRB approval, 35 women with metastatic and locally recurrent ERP BC were included. Selective sequence analysis of the PGR gene was carried out on isolated tumor DNA. The OS from the time of metastatic diagnosis and correlations between mutation status and clinic pathologic elements were examined. There have been few reports of prognostic markers using differentially expressed genes (DEGs) between ERP and ERN BC. They sought to identify significant DEGs associated with ER status and investigate possible prognostic variables for individuals with BC that were ER +. The Information System for Annotation, Visualization, and Integrated Discovery service was used to analyze the functional enrichment of DEGs. Using the Searching Tool for the Retrieval of Interacting Genes, interactions between proteins of the DEGs were examined [12].

The study [13] evaluated the performance of the new version of PREDICT to the present version (2.2) and added the predictive influence of PGR status into it. The predictive impact of PR status was determined based on the examination of data from 45,088 European patients with BC from 49 studies in the Breast Cancer Association Consortium. Cox proportional hazard models were utilized to calculate the PR status hazard ratio. An increase in model accuracy and more precise forecasts of the absolute treatment benefits for specific patients have resulted from the addition of the predictive influence of PR status in PREDICT Breasts. A particularly aggressive form of BC, triple-negative breast cancer (TNBC), has a dismal prognosis and reacts variably to therapies. The study looked at the way key receptors that aren't typically expressed in

TNBC are regulated by vorinostat and indole-3-carbinol (I3C). The study's findings demonstrate that vorinostat and I3C modify the re-expression of essential receptors in several TNBC subtypes via various routes and that the molecular profiles of TNBCs might affect these effects [14]. The study [15] assessed the discordance's predictive significance in patients with metastatic breast cancer (MBC). Using immunohistochemistry and fluorescent in situ hybridization, it was possible to identify the expression of the hormone receptor (HR) and the receptor for human epidermal growth factors (HER2) in primary tumors with metastatic potential. The prognosis of MBC may be impacted by differences in HR status between primary and metastatic lesions, and HR conversion has independent prognostic significance.

2. Experimental

The ER and PGR both affect the BCP. There is a possibility of finding ER and PGR cells in BC. PRP BC, or ERP BC, is positive for the hormone receptor. The DDFS, DFS, and S of 1,155 histologically NN BC patients were related in this study with the ER and PGR and the NG and HG of the patients' malignancies. Women with primary operable BC attended the participating facilities in the United States and Canada between April 1976 and January 1984 were assigned at random to one of three treatment groups: lumpectomy, complete mastectomy, paired with breast radiotherapy.

At the very least, any lower two kinds of the node assessed histologically were removed from every one of them during axillary dissections. Information on randomization, protocol design, and the type of surgery performed, breast radiation, patient and tumor characteristics, and other research elements have already been disclosed. Among the 1,855 participants, 1,155 had follow-up results that showed no axillary nodes. According to patient age and marker, Table 3 shows the demographics of the 1,155 patients that contributed data for this study. Although identifying the tumor's ER, PGR, NG, and HG wasn't necessary for protocol eligibility, 70% and 60% of patients, respectively, had access to data on the original tumor's ER and PGR. Either the ER or PGR was identified in 60% of instances. According to 75% of the tumors, NG and HG were collected. The results of the patients in the three research arms were comparable, according to preliminary analysis, within the ER, PGR, NG, and HG categories. Data for the three therapy groups taken together often includes DDFS, DFS, and S to tumors transporters standing, NG, and HG (Table 1).

Table 1: Age and Tumor Marker (TM) Distribution of Patients Providing Data for the Study

No. Patients			
Marker	**≥ 52 yr**	**All**	**≤ 48 yr**
NG			
Good	342	538	197
Unknown	158	279	118
Poor	177	341	163
HG			
Good	253	395	143
Unknown	164	284	121
Poor	264	479	214
PGR			
≥ 9	238	386	149
Unknown	197	453	199
0-8	186	319	134
ER			
≥ 9	345	524	178
Unknown	178	333	154
0-8	154	301	146

The dextran-coated charcoal with an individual saturating dosage, dextran-coated charcoal titrations, and the sucrose-density gradient were all used to quantify ER and PGR in tumor tissues. This study classified patients as ER and PGR negative in value if the tumors had an ER and PGR level of 0 to 8 femtomole each mg of cytosol proteins and as receptors, positivity if it was more than ≥9.

As opposed to HG 1, it is classified for clearly defined tumors; NG 1 represents the most imperfectly differentiated tumors. Grades 2 and 3 illustrate the least imperfectly differentiated tumors. NG 3 describes the lowest well-differentiated tumors, and a categorization scheme for NG comparable to that for HG is used and promoted.

To avoid confusion due to the two distinct classifications, NG and HG excellent in this study refer to moderate and well differentiated tumors, whereas NG and HG bad suggest poorly differentiated tumors. The standards used to determine if a sample was NG and HG, the level of concordance, and other factors have been published.

The estimated proportion of patients with DFS, DDFS, and S has been calculated using actuarial life tables. Assuming DFS is the desired outcome; an event is defined as the first known recurrence of the illness, the appearance

of a new primary malignancy, or dying from a condition other than cancer. In the overall setting of DDFS, a treatment failure that takes place far away might be the initial failure or follow a local, regional loss of treatment. S is calculated using the total number of death, despite the cause.

To determine the relative relevance of ER, PGR, NG, and HG, multivariate studies utilizing the proportional hazard model developed by Cox were conducted, supposing that all of these factors are taken into account at once. The statistical significance of the average life table distribution discrepancies was investigated using an overview X 2 (log-rank) tests. P-values are given for every two-sided assessment of relevance.

3. Results and Discussions

The Compared to patients with ERN tumors, all patients with ERP tumors had substantially longer DFS, DDFS, and S (P =0.004, 0.003, and 0.001) (Figure 1). DFS, DDFS, and S all showed differences of 7% and 8% during five years of follow-up (Table 4). While age was taken into consideration, the difference in DFS between women ≤48 and ≥52 years old was only 5% (P = 0.002) and 7% (P = 0.003), respectively. Only 5% of the DDFS were different in patients ≤48 years (P = 0.007) and 10% in patients ≥52 years (P =0.001).

Positive tumor ER patients outlived patients with negative receptors by 12% in younger women (P = 0.002) and 8% in older women (P = 0.002). The DFS at five years of age was 72% for patients with cancer ER of 11 to 28 fmol and 74% for patients with a cancer ER of ≥ 99 fmol (Table 2). Similar results were found while patients were investigated according to age; among the younger and more senior patients, DFS was 5% and 4%, while DDFS was 1% and 6%. There was a survival difference (7%, P = 0.003) for the benefit of every patient with PGRP cancers. In patients ≤48 years, the difference was 12% (P = 0.005), and in patients ≥52 years, it was 7% (P = 0.008). The prognosis was not consistently better in individuals with greater PGR levels, according to increasing levels of tumor PGR (Table 2).In patients with malignancies that lacked NG (P = 0.002; Figure 2). The differences were 15%, 17%, and 13% after five years of follow-up (Table 3). Both age groups showed comparable results (consistently P 0.002). The variations in DFS and DDFS among patients through HG deficient and HG excellent tumors were similar to patients seen while linked to NG, though the variation in S was reduced (Figure 2; Table 3). The younger and older age groups had a significant difference: P 0.002 overall for the three results in the young generation category and P = 0.002 for DFS, 0.002 with excellent DDFS, and 0.001 for S.

3.1. Relationship between Combinations of TM and Result

The ERs and PGRs were assessed side by side to see whether the combination of the two is an improved predictor of prognosis that ER unaccompanied (Table 4). No appreciable change in DFS or DDFS was seen. The cancer PR was positive or negative, while the cancer ER was 0 to 8 fmol. The 10% variation in S wasn't statistically significant. Patient outcomes were comparable to patients seen with ER alone in tumors with an ER of ≥ nine fmol and a PR of 0 to 8 or ≥ nine fmol. The difference between patients whose ER and PGR agreed (DFS 9%, P = 0.002, DDFS 9%, P = 0.002, and S 14%, P 0.002) was only marginally more significant than the difference between patients who's ER was positive or negative regardless of their PGR. The ER and NG were looked at simultaneously. The inclusion of ER had minimal effect on individuals who had malignancies. The prognosis was better for patients with tumors with poor ER ≥9 fmol than patients with bad NG, although the difference between ER 0 and 8 was significant.The ER and NG of the tumor were looked at concurrently (Figure 3). The addition of ER had no effect on the outcome in individuals with tumors with excellent NG. Still, the distinction was significantly different (P = 0.005). Patients with poor ER and NG 0 to 8 fmol tumors had a worse prognosis than patients with poor ER and NG ≥9 fmol tumors.

3.2. Patients' Results with Unknown TM

The 331 patients with unknown ER often had similar or even better results than those with elevated ER (Table 4). Participants as an entire or either age group were not substantially impacted by the minor differences between the two groups. Patients with unknown PGR had almost similar survival rates, but patients with PR-positive tumors had somewhat lower but not statistically significant DFS (8%, P = 0.002) and DDFS (5%, P = 0.003). Any age group did not find the little variations between the three results notable.

The patients in Table 4 with uncertain tumor NG did better than patients with horrible tumor NG, despite the DFS and DDFS being considerably worse than patients with tumors with excellent NG (P = 0.001 and.005, respectively). The only aspect of their similar results was their survival rate (P = 0.003). Similar to NG, patients with ambiguous HG had DDFS and DFS ratings that were generally in the middle of patients with poor and good HG throughout both age groups. Patients with uncertain HG had DFS and S that were more comparable to patients with excellent HG than to people with bad HG.

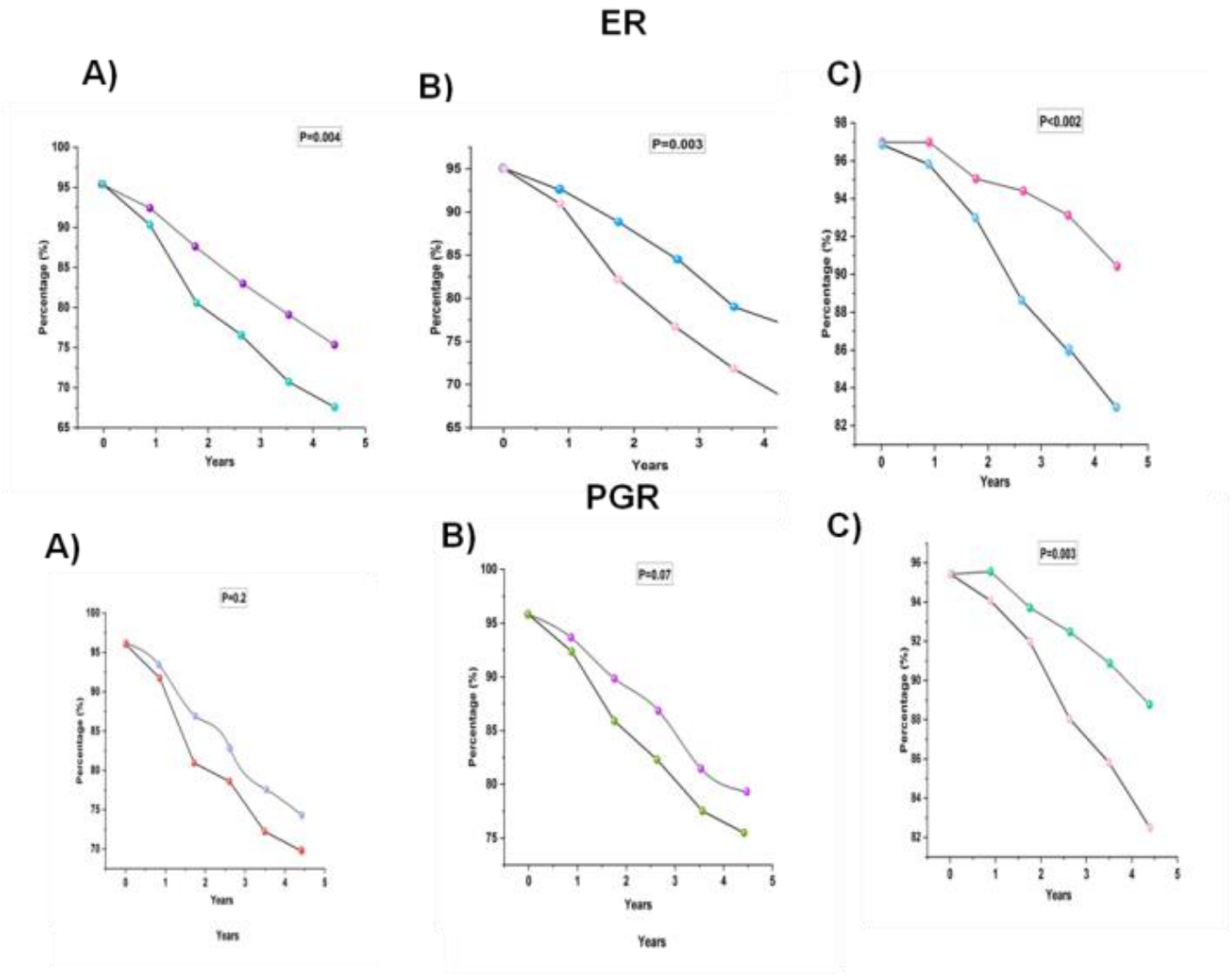

Figure 1: Results of all individuals with tumors that are ER or PR

Table 2: Survival at Five years, the percentage of DFS, and DDFS (Associated with Rising ER or PGR Contents of Tumors)

	PGR				ER			
Receptor (fmol)	**S**	**No of Patients**	**DDFS**	**DFS**	**S**	**No of Patients**	**DDFS**	**DFS**
50-99	88	68	66	73	96	111	76	84
≥ 100	95	195	77	81	93	172	73	83
10-29	83	84	68	82	94	154	74	80
30-49	97	44	72	83	92	92	75	76

Table 3: Percent DFS and DDFSSurvival at Five Years (Related to TM and Age)

	DDFS			S			DFS		
Marker	**≥ 52**	**ALL**	**≤ 48**	**≥ 52**	**ALL**	**≤ 48**	**≥ 52**	**ALL**	**≤ 48**
ER									
≥ 9	83	81	78	91	93	96	77	75	72
Unknown	91	87	83	94	88	84	83	82	78
0-8	73	73	73	82	83	82	69	65	66
PGR									
≥ 9	83	78	74	88	92	95	73	73	68
Unknown	88	85	82	93	89	87	81	81	78
0-8	76	75	73	85	84	82	72	67	64
HG									

Good	87	87	86	92	94	98	82	81	77
Unknown	81	82	82	96	91	89	77	74	74
Poor	75	72	66	83	78	77	65	65	63
NG									
Good	86	87	86	92	92	96	84	85	86
Unknown	82	80	85	96	91	87	77	74	73
Poor	78	74	67	86	85	84	68	68	64

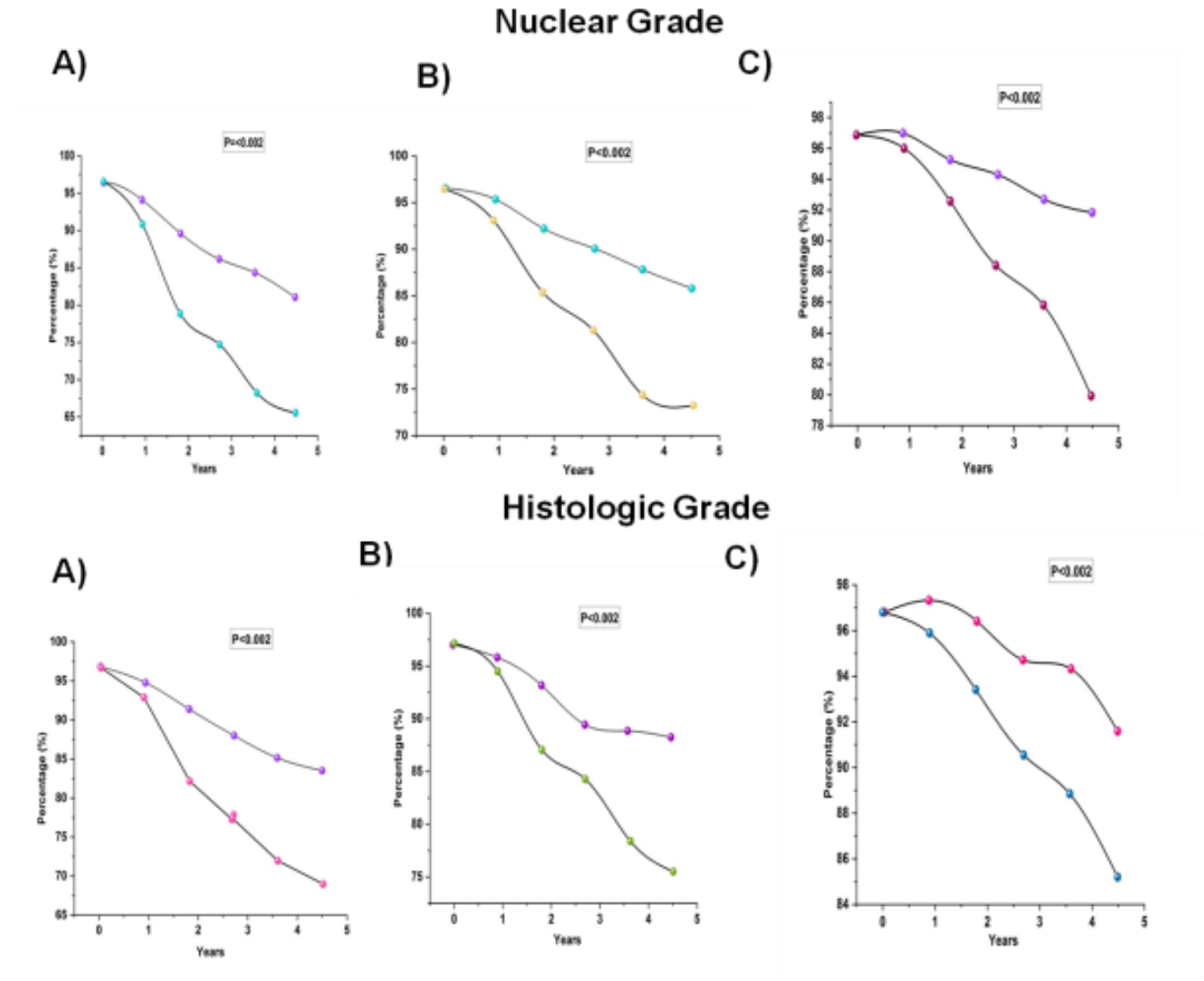

Figure 2: All-patient data for NG or HG cancers

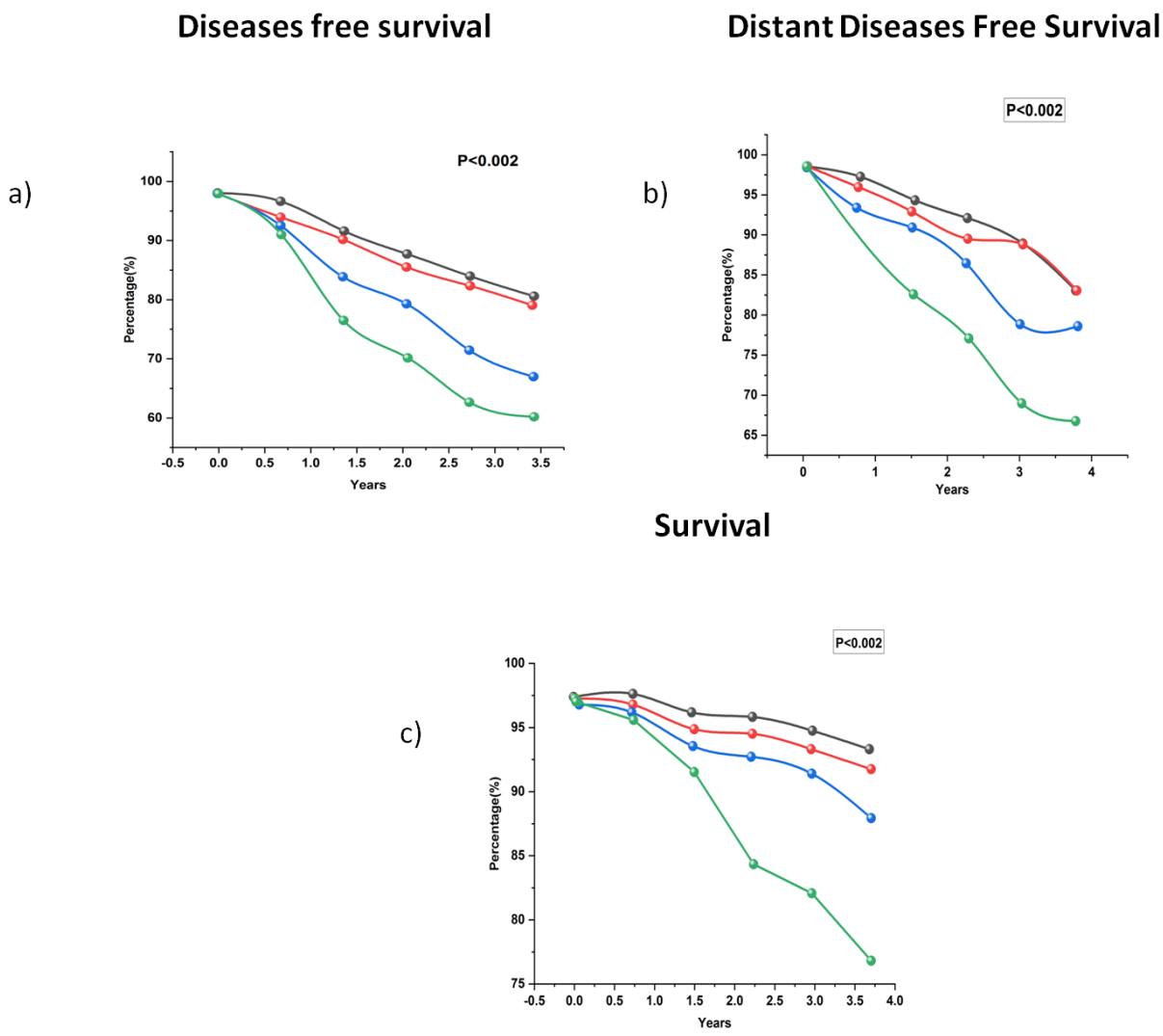

Figure 3: NG and tumor ER results for all patients

Table 4: Percent DFS, DDFS, and endurance at 5 Years (Associated with Tumor ER Both by itself within Combined through PGR)

Receptor					
ER	**DFS**	**No. Patients**	**PGR**	**S**	**DDFS**
0-8	67	54	≥ 9	89	79
≥ 9	75	332	≥ 9	92	78
0-8	65	198	0-8	78	71
≥ 9	74	447	-	93	82
0-8	66	253	-	82	73
≥ 9	76	118	0-8	94	84

Table 5: PGR, ER, HG, and NG Status and TS (All NN Patients)

No. Patients			
Marker	**≥ 52 yr**	**All**	**≤ 48 yr**
NG			

Good	342	538	197
Unknown	158	279	118
Poor	177	341	163
HG			
Good	253	395	143
Unknown	164	284	121
Poor	264	479	214
PGR			
≥ 9	238	386	149
Unknown	197	453	199
0-8	186	319	134
ER			
≥ 9	345	524	178
Unknown	178	333	154
0-8	154	301	146

Table 6: NSABP B-06 Cox Predictive Model for NN Patients

S				**DFS**			**DDFS**		
Predictive Factor	**RR**	**The ratio**	**P Value**	**RR**	**The ratio**	**P Value**	**RR**	**The ratio**	**P Value**
Significant factors only									
HG	-	-	-	-	-	-	0.62	-0.48	.04
NG	0.36	-1.05	<.002	0.82	-0.22	.03	0.51	-0.65.	.003
ER	0.58	-0.55	.04	-	-	-	-	-	-
Four factors									
NG	0.35	-1.02	.002	0.77	-0.26	.02	0.56	-0.61	.009
HG	0.89	-0.13	.71	1.15	0.12	.22	0.63	-0.49	.05
ER	0.58	-0.53	.09	0.95	-0.07	.58	0.76	-0.27	.24
PGR	0.95	-0.05	.88	1.13	0.13	.27	1.25	0.23	.34

3.3. Patient Distribution Based on Marker position and TS

In attendance, no difference in patients with either positive or negative tumor ER was distributed in proportion to TS (Table 5). In each group, 15% of patients developed tumors larger than 1 cm. As a result, fewer individuals with known ER developed tumors between 3.1 and 4.0 cm than patients with unknown ER, which was roughly one-third (30%). Similar results were attained while patients were divided up according to tumor PR and size. Results for patients with good or unknown NG or HG were equivalent, even though NG or HG and TS broke them down. It was shown that both had a higher proportion of patients with tumors measuring 5 cm or more extensive compared to patients with NG or HG-poor tumors.

3.4. The simultaneous variables ER, PGR, NG, and HG are considered.

Single NG provided a considerable (P =.01) self-determining impact on DFS when the four prognostic variables examined in this research were considered collectively (Table 6). While HG (P =.04) and NG (P =.008), to a lesser extent, contributed to DDFS, NG (P =.008) had a significant role in survival. Only the histology parameters associated with differentiation impacted DFS and DDFS, while PR was removed from the model. NG (P 0.001) and ER (P =0.003) were the factors that most significantly influenced survival results.

4. DISCUSSION

The value of systemic treatment in these individuals was assessed later due to the long detained belief that women with BC and NN had a favorable prognosis. Patients with NN may be seen as having better outcomes than individuals with positive nodes, especially when many nodes are present. A 5-year follow-up revealed that 14% of patients were treatment failures, 20% progressed to separated disease, and 15% had gone away. Even less upbeat predictions may be made regarding the destiny of these patients based on patients from B-04 at ten years: 43% had treatment failures, 29% had distant illnesses, and 32% had passed away.

Poor risk-negative node individuals that might benefit from systemic adjuvant treatment have long been recognized as needing identification. Despite the significant lack of agreement in the findings published by multiple researchers, tumor ER has recently been considered discrimination for such an intention.The findings of this study do demonstrate that the efficacy of particular markers as an indication of prognosis in NN patients is questionable, although there are considerable variances in DFS, DDFS, and S-favored women with ERP tumors. There isn't enough of a difference between both receptor types to distinguish between people that may or may not get chemotherapy. The fact that raising tumor ER levels did not reduce the discrepancy in results among patients with ERP and ERN positives tumors is additional proof that cancer ER is not a reliable predictor of prognosis in these people.

It lessens the significance of the receptor for that purpose that age has no bearing on the relationship between tumor ER and patient prognosis. Patient results from regression analysis show that ER contributed in addition to NG only in S. All patients with NN are sufficiently at risk to warrant their inclusion in studies examining systemic adjuvant therapy, as well as to use this type of therapy in the clinical environment for that patient cohort should it be shown to be effective, based on the likelihood of a segregated inability of treatment at five years in 28% of ERN and 20% of ERP patients. The fact that women with cancers with ER or PGR status were unclear and had outcomes comparable to or somewhat better than patients with ER or PGR positive tumors and more favorable than patients with tumors with ER or PGR status harmful is particularly significant.

5. CONCLUSION

The prognosis of patients with ERP and PGRP BC is generally better since these patients are more likely to react to hormone-based treatments like inhibitors. On the other hand, the prognosis of patients with ERN and PRN BC may be worse since these tumors are often more aggressive and less receptive to hormone-based therapies.Patients with ERN and ERP tumors fared better regarding DFS, DDFS, and S (P = 0.004, 0.003, 0.002). However, the differences were relatively slight after five years of follow-up.According to a quickly growing body of research, flow is anticipated to become a more helpful tool for developing improved prognostic indicators and markers for treatment selection. Researchers have widely used it to connect cell cycle kinetics and status to medical and biochemical indicators in BC. The data show that solid proliferative activity, negative tumor ER, and unfavorable histology, such as poor NG or HG, are all closely connected. ER and PGR are the three factors that best predict proliferative activity. Although ER and PGR status play a significant role in deciding BCP, there is a specific limitation. To begin with, not all BC cases can be categorized into groups that are receptor-positive or receptor-negative. Low ER and PGR levels in certain cancers might make them difficult to classify and may impact therapy choices. Future research into the roles of ER and PGR in determining BCP has excellent potential. Creating more accurate and sensitive methods for determining receptor states is one direction that should be explored. Selecting suitable hormonal therapy and predicting treatment results might be improved by increasing the reliability of receptor evaluations.

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