Online: https://jurnal.fk.uisu.ac.id/index.php/ibnusina

Ibnu Sina: Jurnal Kedokteran dan Kesehatan-Fakultas Kedokteran Universitas Islam Sumatera Utara

ISSN 1411-9986 (Print) | ISSN 2614-2996 (Online)

Artikel Penelitian

HUBUNGAN EKSPRESI IMUNOHISTOKIMIA RESEPTOR GLUKOKORTIKOID DENGAN SUBTIPE HISTOPATOLOGI, GRADING, DAN KLASIFIKASI MOLEKULAR PADA PASIEN KANKER PAYUDARA INVASIF

CORRELATION BETWEEN GLUCOCORTICOID RECEPTOR IMMUNOHISTOCHEMICAL EXPRESSION WITH HISTOPATHOLOGICAL SUBTYPE, GRADING, AND MOLECULAR CLASSIFICATION IN INVASIVE BREAST CANCER PATIENTS

Dwi Zahra Putri Joneva[a*], Jessy Chrestella[a], Betty[a], Causa Trisna Mariedina[a], Devi Nafilah Yuzar[a]

[a]Department of Anatomical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Jl. Universitas No.1 Abdul Hakim Building 1st Floor, Medan, 20154, Indonesia

Histori Artikel

Diterima:
20 Juni 2026

Revisi:
22 Juli 2026

Terbit:
1 Januari 2027

Kata Kunci

Kanker payudara invasif, reseptor glukokortikoid, histopatologi, molekular

Keywords

Invasive breast cancer, glucocorticoid receptor, histopathology, molecular

***Korespondensi**

Email:
Zahrajoneva
@gmail.com

A B S T R A K

Paparan stres memicu peningkatkan kortisol yang mengaktifkan respon fisik terhadap sinyal stres dengan berikatan dengan *glucocorticoid reseptor* (GR) yang kemudian mempengaruhi respons imunitas tumor dan resistensi terhadap terapi yang akan memperburuk hasil klinis pasien kanker payudara. Penelitian ini merupakan studi analitik observasional terhadap 60 sampel kanker payudara invasif dari Rumah Sakit Royal Prima dalam periode 2023–2025. Tipe histopatologi karsinoma payudara invasif ditentukan melalui pemeriksaan mikroskopik dan diklasifikasikan menurut WHO 2019. Ekspresi GR dinilai menggunakan *immunoreactive score* (IRS) berdasarkan proporsi sel tumor positif dan intensitas pewarnaan inti. Klasifikasi molekuler ditentukan berdasarkan dari hasil pemeriksaan imunohistokimia ER, PR, HER2, Ki-67 kemudian dikategorikan menurut *American Society of Clinical Oncology* (ASCO) dan *College of America Pathologist* (CAP). Grading histopatologi karsinoma payudara invasive ditentukan berdasarkan *Nottingham grading system*. Data dianalisis secara deskriptif dan analitik menggunakan uji *Kruskal-Wallis*. Pada penelitian ini, terdapat hubungan bermakna antara ekspresi GR dengan grading histopatologi (p=0,040). Ekspresi GR berhubungan dengan diferensiasi yang buruk dan aktivitas proliferatif tumor yang diklasifikasikan berdasarkan grading histopatologi.

A B S T R A C T

Stress exposure triggers an increase in cortisol which activates physical response to stress signals by binding to glucocorticoid receptor (GR) which then affects tumor immune response and therapy resistance that will worsen the clinical outcomes of breast cancer patients. This study is an observational analytical study of 60 invasive breast cancer samples from Royal Prima Hospital in the period 2023–2025. The histopathological type of invasive breast carcinoma was determined through microscopic examination and classified according to WHO 2019. GR expression was assessed using immunoreactive score (IRS) based on proportion of positive tumor cells and intensity of nuclear staining. Molecular classification was determined based on immunohistochemical examination results of ER, PR, HER2, Ki-67 and then categorized according to American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP). Histopathological grading of invasive breast carcinoma was determined based on Nottingham grading system. Data were analyzed descriptively and analytically using the Kruskal-Wallis test. In this study, there was a significant association between GR expression and histopathological grading (p=0.040). GR expression is associated with poor differentiation and proliferative activity of tumors categorized by histopathological grading.

DOI: http://doi.org/10.30743/ibnusina.v26i1.1358

PENDAHULUAN

Breast cancer is second most common type of cancer worldwide after lung cancer.[1] Data from Global Cancer Observatory (GLOBOCAN) in 2022 showed that breast cancer in women ranks second as leading cause of cancer incidence worldwide with an estimated of 2.3 million new cases, which is 11.6% of all cancer cases.[2] Based on 2024 annual reports, breast cancer in Indonesia ranks first, with 66,271 new cases and a breast cancer prevalence of 151.3 per 100,000 population.[3]

Exposure of stress is have a role in etiology of breast cancer.[4] Epidemiological and clinical studies provide strong evidence of correlation between chronic stress and increased risk of cancer incidence and death.[5] Repeated exposure to most stressors increases expression of Corticotrophin Releasing Hormone (CRH) gene and protein in hypothalamus which stimulates release of adrenocorticotropic hormone (ADH) from anterior pituitary gland. ADH relay signals to adrenal cortex and produce cortisol, known as the "stress hormone." Cortisol then triggers a physical response to stress signals by binding to a cytoplasmic receptor, glucocorticoid receptor (GR), which promotes the breakdown of proteins, fats, and carbohydrates. Elevated stress hormones will affect the tumor's immune response and therapy resistance that worsen clinical outcomes in cancer patients.[6]

In breast cancers expressing estrogen receptors (ER-positive), glucocorticoid receptor activation often results in antiproliferative effects. Glucocorticoid receptors can suppress transcription of ER target genes, inhibit estrogen-mediated proliferation pathways, and increase apoptosis. This explains why high GR expression in ER-positive breast cancers often correlates with a better prognosis**.** Otherwise, in triple-negative breast cancer (TNBC), or ER-negative breast cancer, activation of glucocorticoid receptor actually triggers oncogenic pathways such as Wnt, Hippo, and SGK1, which increase proliferation, invasion, metastasis, and resistance to chemotherapy. In this context, GR worsening disease course, therefore high GR expression is often associated with a poor prognosis.[7]

A large-scale study by Tsourlakis et al., using tissue microarray analysis of over 1,700 breast cancer cases, confirmed that GR expression is present in nearly all classic histopathological subtypes (ductal, lobular, medullary, tubular, and mucinous) with varying intensity distribution. In invasive breast carcinoma of no special type (IBC-NST) cases, GR expression increases in low-grade tumors, although this correlation is not always statistically significant.[8] Stress hormones can have a significant influence on cancer cell dynamics and potentially affect the effectiveness of breast cancer therapy.[9]

The biological role of GR appears to differ across histopathological subtypes, with expression often decreasing in invasive ductal tumors, while expression may persist higher in invasive lobular tumors and some specific variants. This emphasizes that clinicopathological interpretation of GR should consider not only hormonal status but also histological morphology and tumor grade.[8–10]

Considering the occurrence both worldwi de and in specific regions, along with scarce studies investigating the correlation between glucocorticoid receptors in breast cancer patients with histopathological subtypes, grading, and molecular classification, researchers are interested to assess this topics.

METHODS

This is a descriptive analytical study with a cross-sectional approach conducted in Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Sumatera Utara (USU), from July 2025 to April 2026. The study was conducted after obtaining permission from Research Ethics Committee of USU which number is 204/UN5.2.1.1.42/SPB/2025. All information related to this study is intended solely for educational purposes and medical science development of Anatomical Pathology Department.

Study samples

This study population were all patients diagnosed histopathologically and undergoing molecular subtyping examination as invasive breast cancer patients at Royal Prima Hospital Medan. Total of 60 samples were obtained from paraffin slides/blocks of breast cancer patients diagnosed histopathologically with hematoxylin-eosin (HE) staining as invasive breast cancer, which were derived from post-operative preparations that met inclusion and exclusion criteria (random sampling).

The inclusion criteria were adequate clinical data from medical records, including age, and immunohistochemical examination of ER, PR, HER2, and Ki-67; slides or paraffin blocks of patients with invasive breast carcinoma diagnosed histopathologically, derived from post-operative preparations with HE staining and adequate molecular subtyping of invasive breast carcinoma after re-evaluation. The exclusion criteria were tumor tissue in preparations which was too minimal (more stroma than tumor mass of at least 100 tumor cells) or paraffin blocks that were damaged or missing which causes immunohistochemical examination could not be performed.

Histopathological type

The histopathological type of invasive breast carcinoma is determined through microscopic examination and classified according to WHO 2019. Invasive breast carcinoma of no special type (IBC-NST), if the tumor with tumor cells arranged in a pattern of cords, nests and trabeculae but does not meet the characteristics required to be established as a specific histological type, such as lobular carcinoma or tubular carcinoma. Invasive lobular carcinoma (ILC), a tumor consisting of discohesive cells in the form of individual cells or arranged in a linear and targetoid single file pattern in a fibrous stroma. Mixed invasive breast carcinoma that shows two or more different histological types of invasive carcinoma in one tumor lesion, and each type must contain a component of ≥10% of tumor. Others, invasive breast subtypes other than IBC NST, ILC, and Mixed invasive breast carcinoma.

Immunohistochemical expression of glucocorticoid receptor

Paraffin block cutting and preparation of HE-stained slides. The HE slides were evaluated

by researcher and two anatomical pathologists in a double-blind manner to determine histopathological type and grade. Serial sections of paraffin blocks were used to obtain one slide, which was then stained with glucocorticoid receptor immunohistochemistry.

The immunohistochemical expression of GR in this study used Genetex immunohistochemical staining, GTX101120 North America is a polyclonal antibody that uses rabbits as its host, using a dilution of 1:100- and diethylaminobenzene (DAB). The staining results were displayed positively as a brown color in the cell nucleus, using placental tissue as a positive control.

The immunohistochemical staining results for glucocorticoid receptors were assessed using Immunoreactive Score (IRS). The IRS is a semi-quantitative immunohistochemical scoring system that assesses antigen expression based on two components: the percentage of tumor cells showing a positive reaction and staining intensity. The final score is obtained by multiplying these two components, with a score range of 0–12.

Results Interpretation :[21]

Proportion of positive cells	Staining intensity	Total IRS = proportion × intensity
0 = 0%	0 = negative	0 = negative
1 = <10%	1 = weak	1–3 = weak
2 = 10–50%	2 = moderate	4–8 = moderate
3 = 51–80%	3 = strong	9–12 = strong
4 = >80%		

Molecular classification

Molecular classification is based on immunohistochemical examinations results of ER, PR, HER2, and Ki-67, then categorized according to American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP). In this study, molecular classification was divided into three groups which is Luminal, HER2 Enriched, and Triple Negative. (Table 1)

Tabel 1. Molecular classification.

Molecular Subtypes	Receptor Status			
	ER	PR	HER2	Ki-67
Luminal A	+	+	-	Low
Luminal B-like (HER2- Negative)	+	(-) or low	-	High
Luminal B-like (HER2- Positive)	+	Any	Overexpressed or amplified	Any
HER2 Positive (non luminal)	-	-	Overexpressed or amplified	
Triple negative	-	-	-	

Histopathology grading

Histopathological grading of invasive breast carcinoma (ordinal scale) used Nottingham grading system. Tumor grade was determined by microscopic assessment (Olympus CX43). In this study, three parameters were used:

Tubular/glandular formation was scored 1 if tubular formation was found in > 75% of tumor; 2 if tubular formation was found in 10-75% of tumor; 3 if tubular formation was only 10% of tumor.

Nuclear pleomorphism was scored 1, indicating small, regular, and uniform cells; 2

indicating a moderate increase in nuclear size and variation; 3 indicating highly variable nuclear size and shape.

The number of mitoses was determined by summing all definite mitotic figures found in 10 large fields (400x). Because the microscope used in this study has a diameter of 0.5 mm, the mitotic activity assessment is 1 for a mitosis count of ≤7/10 low-power magnification (LPB); 2 for a mitosis count of 8-14/10 LPB; 3 for a mitosis count of ≥15/10 LPB.

The scores for each parameter will be accumulated and interpreted as follows:

1 = Grade 1, if the sum of the scores is 3-5.

2 = Grade 2, if the sum of the scores is 6 or 7.

3 = Grade 3, if the sum of the scores is 8 or 9.

Statistical Analysis

Descriptive analysis was used to assess frequency distribution of age groups, histopathological subtypes, grading, molecular classification, and immunohistochemical expression of glucocorticoid receptors. Statistical tests based on age groups, histopathological subtypes, grading, and molecular classification on immunohistochemical expression of glucocorticoid receptors with an interval measurement scale using Kruskal-Wallis test.

RESULTS

The study used 60 samples that met inclusion and exclusion criteria. After slides review, all samples were sourced from Royal Prima Hospital. Breast excisional biopsies, as well as immunohistochemical slides for ER, PR, HER2, and Ki-67, were collected on periode 2023–2025.

The frequency distribution and analysis of invasive breast carcinoma (IBC) patients in this study found majority of patients were aged 40–49 years (36.7%), had invasive breast carcinoma of no special type (IBC-NST) histopathological subtype (66.7%), luminal molecular classification (83.33%), and were classified as histopathological grade 3 (63.33%). (Table 2)

Table 2. Frequency distribution and analysis of IBC patients based on age group, histopathological subtype, molecular classification and histopathological grading system.

No	Characteristics	N	%
1.	**Age groups**		
	<30 years old	0	0
	30 – 39 years old	4	6,7
	40 – 49 years old	22	36,7
	50 – 59 years old	20	33,3
	≥60 years old	14	23,3
2.	**Histopathological subtypes**		
	IBC NST	41	68,3
	ILC	9	15
	Mixed Invasive Breast Carcinoma	7	11,6
	Others	3	5
3.	**Molecular Classification**		
	Luminal	50	83,33
	HER2 Enriched	6	10
	TNBC	4	6,67
4.	**Histopathological grading**		
	Grade 1	1	1,67
	Grade 2	21	35
	Grade 3	38	63,33
	Total sampel	60	100

The frequency distribution of glucocorticoid receptor immunohistochemical expression in invasive breast carcinoma found highest proportion for moderate expression (36.7%), followed by weak expression (30%) and strong expression (23.3%). Only 6 cases (10%) did not express glucocorticoid receptors. (Table 3)

Table 3. Frequency distribution of immunohistochemical expression of glucocorticoid receptor in invasive breast carcinoma.

Characteristics	N	%
Glucocorticoid receptor expression		
Negative	6	10
Weak	18	30
Moderate	22	36,7
Strong	14	23,3
Total	60	100

Based on age, a p-value of 0.806 was obtained, indicating no significant correlation between patient age and glucocorticoid receptor expression. Descriptively, glucocorticoid receptor expression appeared to be distributed across all age groups without a consistent pattern of increase or decrease. This supports the statistical test results that age was not significantly factor associated with variations in glucocorticoid receptor expression in this study. (Table 4)

In analysis of correlation between IBC subtype and glucocorticoid receptor expression, statistical test results were declared not applicable (N.A.). This indicates that correlation between the two variables could not be statistically assessed in this study. Descriptively, these data show that glucocorticoid receptor expression can be found in various histopathologic subtypes, but the predominance of IBC-NST cases is likely influenced by proportion of this subtype, which is indeed the most common in the study sample. (Table 4)

Analysis on molecular classification obtained a p-value of 0.246, indicating no statistically significant correlation with glucocorticoid receptor expression. Although descriptively, luminal group appears to dominate all receptor expression categories, this is likely related to significantly higher number of luminal cases compared to other molecular groups. Therefore, molecular classification has not been statistically proven to be associated with glucocorticoid receptor expression in this study. (Table 4)

Table 4. Correlation of glucocorticoid receptor expression with age, IBC subtype, molecular classification, and histopathological grading.

No	Variable	Glucocorticoid Receptor Expression (gene: NR3C1)								P value*
		Negative		Weak		Moderate		Strong		
		N	%	N	%	N	%	N	%	
1.	**Age (years old)**									0,806
	30-39	0	0	2	11,1	1	4,6	1	7,1	
	40-49	3	50,0	6	33,3	9	40,9	4	28,6	
	50-59	0	0	6	33,3	9	40,9	5	35,7	
	≥60	3	50,0	4	22,3	3	13,6	4	28,6	
2.	**IBC subtype**									N. A.
	IBC NST	4	66,6	11	61,1	14	63,6	12	85,8	
	ILC	1	16,7	5	27,7	3	13,6	0	0	
	Mixed Invasive Breast Carcinoma	1	16,7	1	5,6	4	18,2	1	7,1	
	Others	0	0	1	5,6	1	4,6	1	7,1	
3.	**Molecular classification**									0,246
	Luminal	4	66,7	17	94,4	19	86,4	10	71,4	
	HER2 Enriched	2	33,3	1	5,6	1	4,5	2	14,3	
	TNBC	0	0	0	0	2	9,1	2	14,3	
4.	**Histopathological Grading**									**0,040**
	Grade 1	0	0	1	5,6	0	0	0	0	
	Grade 2	2	33,3	9	50,0	9	40,9	1	7,1	
	Grade 3	4	66,7	8	44,4	13	59,1	13	92,9	

* Kruskal-Wallis test

Analysis of histopathological grading variable obtained a p-value of 0.040, indicating a statistically significant correlation between histopathological grading and glucocorticoid receptor expression (Table 4). This finding indicates that strong glucocorticoid receptor expression was most commonly found in grade 3 tumors, while weak to moderate expression was more common in grade 2 tumors. In other words, there was a tendency that the higher histopathological grading, the greater proportion of cases with strong glucocorticoid receptor expression. This result is important because it indicates a possible correlation between glucocorticoid receptor expression and higher histological malignancy in this study population.

DISCUSSION

Stress hormones such as corticosterone (CORT), through glucocorticoid receptors (GR), play a role in the development of cancer cells, especially in breast cancer, where the presence of CORT is categorized as an endocrine malignancy.[11] Nuclear GR was positively correlated with CK5/6 expression, a basal phenotype marker, although no significant relationship was found between GR expression and histopathological grading.[8] Invasive breast carcinoma is a heterogeneous disease, both morphologically, immunohistochemically, and molecularly. Estrogen receptor status plays a key role in distinguishing the luminal subtype from other molecular phenotypes.[12]

In this study, majority of cases showed detectable glucocorticoid receptor expression, with largest distribution in moderate category, followed by weak and strong, while cases with negative expression were relatively few. This finding is essentially consistent with current understanding that glucocorticoid receptor (GR or NR3C1) is a receptor that is quite frequently expressed in breast cancer, but its biological and clinical significance is highly dependent on the molecular context, particularly ER status. Recent studies have suggested that GR plays a contextual role in ER-positive breast cancer, where GR activity can suppress proliferation through GR-ER interactions. Whereas in ER-negative and TNBC, GR activation is more frequently associated with survival pathways, epithelial-mesenchymal transition (EMT), migration, and metastasis.[10,13,14] Therefore, the presence of GR expression in this study cannot be interpreted uniformly as a good or bad factor, but must be interpreted in context of molecular subtype composition and histopathological characteristics of the studied cohort.

Biologically, the glucocorticoid receptor is a nuclear receptor that, in its inactivated state, is generally located in cytoplasm. It then migrates to the nucleus after binding to glucocorticoid ligands and regulates transcription of various genes related to proliferation, apoptosis, inflammation, metabolism, migration, and cellular stress responses.[13] In breast cancer, the role of GR is contextual. In estrogen receptor-positive breast cancer, GR activation has been reported to interact with the ER pathway and is associated with decreased proliferation and a more indolent tumor phenotype. Conversely, in ER-negative breast cancer and TNBC, GR activation is more frequently associated with increased migration,

tumor cell survival, chemotherapy resistance, and a poorer prognosis.[13,14]

This study not found significant correlation between age and glucocorticoid receptor expression. These results indicate that variation in GR expression in this cohort was not influenced by the age distribution of patients. Biologically, these findings remain applicable because GR expression and activity in breast cancer are more influenced by transcription factors, hormone receptor status, and tumor subtype-specific cellular programs than by chronological age alone.[7,13] In breast cancer, age is associated with incidence and overall clinical outcome, but not necessarily directly with expression levels of specific biomarkers in tumor tissue.

These results align with Al-Alem et al. study, which reported that GR expression in breast cancer tissue was not associated with key clinicopathologic characteristics.[10] Similar findings were also seen in Matossian et al. study of early-stage TNBC, where no significant correlation between GR expression and age was found.[15]

In this study, correlation between the IBC histopathological type and glucocorticoid receptor expression could not be statistically assessed, therefore the results are declared not applicable (N.A.). Based on the data distribution, the majority of cases were invasive breast carcinoma of no special type, representing 41 of 60 cases (68.3%), while invasive lobular carcinoma accounted for only 9 cases (15.0%), mixed invasive breast carcinoma for 7 cases (11.7%), and others for only 3 cases (5.0%). Cross-tabulations of glucocorticoid receptor expression also revealed that some category combinations had very low, even zero, frequencies. For example, invasive lobular carcinoma was not found in the strong expression category, and others were not found in the negative expression category. This distribution resulted in uneven and sparse data distribution between cells which caused statistical analysis impossible.

Descriptively, glucocorticoid receptor expression at all intensity levels was still dominated by IBC-NST. In the negative expression category, this subtype comprised 4 cases (66.6%), 11 cases (61.1%) of weak expression, 14 cases (63.6%), and 12 cases (85.8%) of strong expression. Meanwhile, ILC was primarily found in weak and moderate expression, but not in strong expression. Mixed invasive breast carcinoma was distributed across all expression categories, but its number was small, while the other group consisted of only one case in each of the weak, moderate, and strong categories. This figure indicates that although descriptively there is variation in the distribution of glucocorticoid receptor expression within each histopathological type, the number of cases in some groups is too small to allow for an inferential assessment of the correlation.

Therefore, the N.A. result for this variable does not imply a biological relationship between histopathological type and glucocorticoid receptor expression, but rather indicates that the available data are insufficient for statistical analysis. This is primarily due to the disparity in sample size between histopathological subtypes and presence of some cells with very low or zero

frequencies in the cross-tabulation. Therefore, interpretation of this variable can only be done descriptively, and not statistically inferentially.

This study found that molecular classification was not significantly associated with glucocorticoid receptor expression (p=0.246). Descriptively, GR expression was found across all molecular groups, but there was no distributional difference strong enough to achieve statistical significance. These results align with Al-Alem et al. study, which also found no consistent association between GR expression and key clinicopathologic characteristics of breast cancer.[10] In the context of study cohort, this nonsignificant result is likely influenced by the highly skewed sample distribution, as the majority of cases were in the luminal group, while the HER2-enriched and, especially, triple-negative groups were much smaller. This situation reduces analysis power to detect significant differences between subtypes.

On the other hand, these results may also be considered at odds with current biological understanding, which emphasizes that GR function is highly dependent on breast cancer subtype. Studies by Butz et al.[6], Clark and Conzen[13], and GR isoform study by Butz et al.[12] confirm that in ER-positive cases, GR tends to be anti-proliferative, whereas in ER-negative or TNBC it is more associated with an aggressive program. A study by Prekovic et al. even showed that GR activity status contributes to luminal subtype identity.[16] Therefore, the lack of significance in this study is more appropriately interpreted as a lack of evidence of an association in this cohort, rather than evidence that molecular subtype does not influence the role of GR at all.

The most important finding of this study was a significant correlation between histopathological grading and glucocorticoid receptor expression. Strong GR expression was most common in Grade 3 tumors, while Grade 2 tumors were more likely to be weak and moderate. This suggests that increased GR expression tends to be associated with higher histologic grades tumors.

These results are explained by the concept that GR has a more diverse biological role. In more aggressive tumors, GR activation can contribute to increased cell survival, stress resistance, altered cell adhesion, activation of migration programs, and EMT.[12,13] Clark and Conzen's study confirmed that GR oncogenic activity depends on breast cancer subtype. ER-positive GR tends to be associated with a more indolent phenotype, whereas in ER-negative or TNBC, GR is more closely associated with tumor aggressiveness.[13] The findings of Matossian et al. study, which showed that high GR expression in early-stage TNBC is associated with higher T-regulatory infiltration, and Kumar et al. study, which confirmed the association of GR with decreased survival and increased risk of metastasis in TNBC, further strengthen the possibility that GR, in certain contexts, is indeed associated with more aggressive tumor biology.[13,17]

However, these results contradict some previous literature suggesting that GR expression in breast cancer, particularly ER-positive breast cancer, is associated with lower grade and better outcomes. The classic

Abduljabbar et al. study reported that GR levels tend to decrease with cancer progression, while more recent sources also confirm that in early-stage ER-positive breast cancer, higher GR expression is associated with lower tumor grade and better outcomes.[8–10] The discrepancy between this study and those studies results is likely influenced by several factors. First, the molecular groups in this study were combined into luminal, thus obscuring the biological distinction between luminal A and luminal B, even though GR activity within the luminal spectrum can vary.[12,13] Second, this cohort was predominantly grade 3, therefore association may better reflect a distribution of samples heavily weighted toward aggressive tumors. Third, semiquantitative immunohistochemistry-based GR assessment is influenced by antibody clones, antigen retrieval techniques, cut-offs, and whether nuclear location alone or a combination of other patterns is assessed.[12] Therefore, these results should not be directly interpreted as contradictory to previous literature, but rather as evidence that significance of GR in breast cancer is strongly influenced by biological context of the cohort studied.

In estrogen receptor-positive breast carcinomas, particularly the luminal subtype, GR generally interacts with the estrogen receptor (ER) through a crosstalk mechanism. GR activation can suppress ER transcriptional activity, thereby reducing the expression of genes related to cell proliferation and the cell cycle. Therefore, in luminal tumors, GR expression is often associated with better tumor differentiation and a better prognosis.[16] GR expression in TNBC may be associated with a worse prognosis compared to luminal tumors. A review by Bakour et al. also stated that in early-stage untreated TNBC, high GR expression is associated with cancer progression and a worse prognosis.[18] GR can act as a tumor suppressor in ER-positive breast cancer, but plays a role as an oncogenic driver in ER-negative breast cancer, including triple-negative breast cancer (TNBC). Therefore, the interpretation of GR expression in invasive breast carcinoma should always consider the molecular subtype because its biological significance is not universal, but is influenced by interactions with different signaling pathways in each subtype.[19,20]

This study found a correlation between glucocorticoid receptor expression and histopathological grading of breast cancer. However, the study has limitations which is small sample size and uneven data distribution hindered comprehensive statistical analysis. Furthermore, cross-sectional design of this study obscured the validity of correlation between two variables and limited results generalizability. This study neither conduct multivariate analysis nor evaluate confounding factors that might influence the results, therefore results cannot be used as a reference.

CONCLUSION

Glucocorticoid receptor expression is associated with poor differentiation and proliferative activity of tumors categorized by histopathological grading.

ACKNOWLEDGEMENTS

The authors would like to thank the supervisor and staff of Department of Anatomical Pathology, Faculty of Medicine,

Universitas Sumatera Utara who provided guidance and supportive input during completion of this research. The authors also expresses gratitude to all parties involved. However, authors acknowledges the limitations of this study, which necessitates future research that can help evaluate and support the findings.

REFERENCES

1. American Cancer Society. *Breast Cancer Facts & Figures 2024--2025*. Atlanta: American Cancer Society, Inc.; 2024. Available from: https://share.google/5OfAQxygoGrUOJgJZ. Accessed June 7, 2026.
2. Bray F, Laversanne M, Sung H, et al. Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2024;74(3):229-263. doi:10.3322/caac.21834
3. Kementerian Kesehatan Republik Indonesia. Strategi Indonesia dalam Upaya Melawan Kanker. 2024. Available from:https://repository.kemkes.go.id/book/1379. Accessed June 7, 2026.
4. Vignjević Petrinović S, Milošević MS, Marković D, Momčilović S. Interplay between stress and cancer—A focus on inflammation. *Front Physiol*. 2023;14. doi:10.3389/fphys.2023.1119095
5. Moore JX, Andrzejak SE, Bevel MS, Jones SR, Tingen MS. Exploring racial disparities on the association between allostatic load and cancer mortality: A retrospective cohort analysis of NHANES, 1988 through 2019. *SSM - Popul Heal*. 2022;19. doi:10.1016/j.ssmph.2022.101185
6. Vignjević Petrinović S, Milošević MS, Marković D, Momčilović S. Interplay between stress and cancer—A focus on inflammations. *Front Physiol*. 2023;14. doi:10.3389/fphys.2023.1119095
7. Butz H, Patócs A. Mechanisms behind context-dependent role of glucocorticoids in breast cancer progression. *Cancer Metastasis Rev*. 2022;41(4):803-832. doi:10.1007/s10555-022-10047-1
8. Tsourlakis MC, Kind S, Dwertmann Rico S, et al. Glucocorticoid Receptor (GR) Expression in Human Tumors: A Tissue Microarray Study on More than 14,000 Tumors. *Biomedicines*. 2025;13(7). doi:10.3390/biomedicines13071683
9. Mitre-Aguilar IB, Moreno-Mitre D, Melendez-Zajgla J, et al. The Role of Glucocorticoids in Breast Cancer Therapy. *Curr Oncol*. 2023;30(1):298-314. doi:10.3390/curroncol30010024
10. Al-Alem U, Mahmoud AM, Batai K, et al. Genetic Variation and Immunohistochemical Localization of the Glucocorticoid Receptor in Breast Cancer Cases from the Breast Cancer Care in Chicago Cohort. *Cancers (Basel)*. 2021;13(10):2261. doi:10.3390/cancers13102261
11. Mitre-Aguilar IB, Moreno-Mitre D, Melendez-Zajgla J, et al. The Role of Glucocorticoids in Breast Cancer Therapys. *Curr Oncol*. 2023;30(1):298-314. doi:10.3390/curroncol30010024
12. Ross DS, Pareja F. Molecular Pathology of Breast Tumors: Diagnostic and Actionable Genetic Alterations. *Pathology*. 2022;14(3):455-457. doi:10.1016/j.path.2021.05.009
13. Butz H, Vereczki V, Budai B, et al. Glucocorticoid Receptor Isoforms in Breast Cancer Raise Implications for Personalised Supportive Therapies. *Int J Mol Sci*. 2024;25(21):11813. doi:10.3390/ijms252111813
14. Clark AB, Conzen SD. Glucocorticoid receptor-mediated oncogenic activity is dependent on breast cancer subtype. *J Steroid Biochem Mol Biol*. 2024;243. doi:10.1016/j.jsbmb.2024.106518
15. Matossian MD, Shiang C, Dolcen DN, et al. High Tumor Glucocorticoid Receptor Expression in Early-Stage, Triple-Negative Breast Cancer Is Associated with Increased T-Regulatory Cell Infiltration. *Breast Cancer Res Treat*. 2025;209(3):563-572. doi:10.1007/s10549-024-07515-3

16. Prekovic S, Chalkiadakis T, Roest M, et al. Luminal Breast Cancer Identity Is Determined by Loss of Glucocorticoid Receptor Activity. *EMBO Mol Med*. 2023;15(12):e17737. doi:10.15252/emmm.202317737
17. Kumar R. Role of Glucocorticoid Receptor in Triple-Negative Breast Cancer. *Receptors*. 2025;4(2):8. doi:10.3390/receptors4020008
18. Bakour N, Moriarty F, Moore G, Robson T, Annett SL. Prognostic Significance of Glucocorticoid Receptor Expression in Cancer. *Cancers (Basel)*. 2021;13(7):1649. doi:10.3390/cancers13071649
19. Effah W, Ponnusamy S, Asemota S, Khosrosereski Y, Narayanan R. Context Dependent Role of Glucocorticoids in Breast Cancer. *Cancer Res*. 2024;84(6). doi:10.1158/1538-7445.AM2024-6281
20. Gandhi S, Elkhanany A, Oshi M, et al. Contribution of immune cells to glucocorticoid receptor expression in breast cancer. *Int J Mol Sci*. 2020;21(13):1-17. doi:10.3390/ijms21134635
21. Baker GM, Murphy T, Block T, Nguyen D, Lynch FJ. Development and validation of an immunohistochemistry assay to assess glucocorticoid receptor expression for clinical trials of mifepristone in breast cancer. Cancer Manag Res 2015;7:361–368