Rom J Morphol Embryol 2025, 66(4):645–652 ISSN (print) 1220–0522, ISSN (online) 2066–8279 doi: 10.47162/RJME.66.4.02

ORIGINAL PAPER

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Immunohistochemical predictors of local recurrence in breast carcinoma: development and sensitivity validation of an IHC-based risk score

VALENTINA CĂLUIANU[1)], LAURENŢIU AUGUSTUS BARBU[2,3)], GABRIEL FLORIN RĂZVAN MOGOŞ[2,3)], NICOLAE DRAGOŞ MĂRGĂRITESCU[2,4)], DANIELA MARINESCU[2,4)], STELIAN ŞTEFĂNIŢĂ MOGOANTĂ[2,4)], LIVIU VASILE[2,4)], LILIANA CERCELARU[5,6)], IOANA-ALEXIA ŢENEA-COJAN[7)], TIBERIU ŞTEFĂNIŢĂ ŢENEA-COJAN[2,3)]

[1)]*Doctoral School, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania*

[3)]*Department of Surgery, Railway Clinical Hospital, Craiova, Romania*

[4)]*Department of Surgery, Emergency County Hospital, Craiova, Romania*

[5)]*Department of Anatomy and Embryology, University of Medicine and Pharmacy of Craiova, Romania*

[6)]*Department of Pathology, Emergency County Hospital, Craiova, Romania*

[7)]*Student, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Background: Local recurrence after breast-conserving surgery (BCS) remains clinically relevant and is associated with poorer long-term outcomes. While several prediction tools exist, many rely on costly genomic assays or omit key biological variables routinely assessed by immunohistochemistry (IHC). *Patients, Materials and Methods*: We retrospectively analyzed 100 consecutive patients with invasive breast carcinoma treated by BCS (2013–2018). IHC data included estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) [0–3+, with 2+ confirmed by chromogenic *in situ* hybridization (CISH)], as well as hormonal phenotypes. Local recurrence occurred in 21 cases. An integrated IHC score (0–6 points) was constructed using weighted biological predictors (ER-, PR-, HER2+, and ER-/PR- phenotype), stratifying cases into low (0–2), moderate (3–4), and high (≥5) risk categories. Although ER, PR, and HER2 status were available for all cases, case-level linkage between HER2 positivity and ER/PR phenotypes was not consistently available; therefore, three sensitivity scenarios (optimistic, neutral, and pessimistic) were applied to assess the robustness of the findings. *Results*: Recurrence was higher in biologically unfavorable subgroups: ER- (26.47% *vs.* 9.09% in ER+), PR- (21.42% *vs.* 10.34% in PR+), ER-/PR- phenotype (37.5%), and HER2-positive tumors (33.33% *vs.* 11.36% in HER2-). The integrated score achieved consistent separation of risk categories, with most recurrences concentrated in moderate- and high-risk groups. Sensitivity analyses showed stable stratification across all three HER2 allocation scenarios, supporting the robustness of the model despite uncertainty in HER2- phenotype overlap. *Conclusions*: A pragmatic IHC-based risk score based on routinely available biomarkers stratified local recurrence risk in breast cancer patients treated with BCS and remained stable under sensitivity testing. External validation in larger, multicenter cohorts is warranted.

Keywords: breast carcinoma, local recurrence, estrogen receptor, progesterone receptor, HER2/neu, risk score.

Introduction

Breast cancer remains the most common malignancy among women worldwide, and local recurrence continues to have a major prognostic impact, being strongly associated with increased risk of metastasis and mortality. Clinical data show that patients who develop loco-regional recurrence experience significantly worse survival, underscoring the need for accurate risk prediction and optimal local control [1].

Despite advances in modern therapy, the risk of ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery (BCS) remains clinically relevant, leading to the development of dedicated predictive nomograms [2, 3]. Tumor biology defined by immunohistochemistry (IHC) – estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) – is central to both prognosis and treatment selection. Molecular subtypes differ markedly in local recurrence risk, with ER-/HER2- and triple-negative tumors carrying significantly higher recurrence probability.

This biological stratification is further supported by modern machine-learning (ML) studies, where ER/PR/HER2 status consistently emerges as a key predictive feature [4]. However, current prediction models remain limited. Clinical-only models show moderate performance, while genomic assays, although useful, are costly, not universally available, and fail to identify all high-risk patients. Likewise, ML models based solely on clinical variables underperform compared to multimodal models [5]. Recent evidence

demonstrates that integrating multiple data domains – clinical, biological, and imaging – substantially improves predictive accuracy, with multimodal ML models achieving area under the curve (AUC) values >0.90 [6, 7].

Despite these advances, a clinically applicable model based on immunohistochemical markers, interpreted in the context of core clinical variables specifically for predicting local recurrence remains unavailable, as most existing tools emphasize distant relapse or omit key biological markers. Given the prognostic significance of local recurrence and the central role of ER/PR/HER2, such a tool is needed to improve individualized treatment, particularly radiotherapy (RT) and BCS decisions.

Aim

The aim of this study was to develop and validate an IHC-based score for predicting local recurrence in patients with breast cancer.

Patients, Materials and Methods

Study population

The study included 100 consecutive patients diagnosed with invasive breast carcinoma and treated with BCS at the Department of Surgery, Railway Clinical Hospital, Craiova, Romania, between 2013 and 2018. For each case, complete immunohistochemical data were available, including ER, PR, and HER2 status [scored 0–3+ by IHC, with 2+ cases confirmed by chromogenic *in situ* hybridization (CISH)], as well as the four major hormonal phenotypes (ER+/PR+, ER-/PR-, ER+/PR-, ER-/PR+). Additional histopathological variables included histological type [no special type (NST), lobular, mixed], Nottingham grade (G1–G3), and pathological tumor, node, metastasis (pTNM) stage. Although histological grade (Nottingham system) and pTNM stage were recorded for all cases, these parameters were not included in the recurrence risk analysis or the score construction, as the primary objective of the study was to evaluate the prognostic impact of immunohistochemical markers. Grading and staging were therefore documented for cohort characterization purposes only. Outcome information consisted of the presence or absence of local ipsilateral recurrence (21 cases *vs.* 79 non-recurrent cases) and the disease-free interval. Patients were eligible for inclusion if they had a histopathologically confirmed diagnosis of invasive breast carcinoma, underwent BCS, had complete ER/PR/HER2 immunohistochemical evaluation, possessed adequate surgical tissue for histological and IHC analysis, and had documented follow-up for local recurrence. Exclusion criteria comprised purely non-invasive lesions, such as ductal carcinoma *in situ* (DCIS) without an invasive component, incomplete IHC profiles (missing ER, PR, or HER2), insufficient tissue for reliable IHC assessment, and incomplete follow-up or complete loss to follow-up.

Immunohistochemical procedures and evaluation

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tumor specimens in the institutional pathology laboratory, according to standard diagnostic protocols in use at the time of treatment. ER, PR, and HER2/neu immunostaining were carried out using validated antibodies routinely employed in clinical practice.

Immunohistochemical reactions were performed using standardized techniques, and staining evaluation was conducted by experienced pathologists as part of routine diagnostic assessment. ER and PR status were assessed based on nuclear staining in invasive tumor cells, while HER2 status was scored on a 0–3+ scale according to contemporary *American Society of Clinical Oncology/College of American Pathologists* (ASCO/CAP) recommendations, with equivocal (2+) cases further evaluated by CISH.

Immunohistochemical scoring and interpretation followed internationally accepted guidelines applicable at the time of diagnosis, ensuring consistency and reproducibility across cases.

Integrated immunohistochemical scoring method

The scoring system was developed specifically for this study, based on the relative prognostic contribution of each biological variable derived from the available cohort data and established literature on local recurrence risk in BCS. Because the present analysis was based exclusively on the immunohistochemical dataset, the IHC-based score was adapted to include only biological predictors that were consistently available for all cases. Each biomarker associated with an increased risk of local recurrence was assigned a weighted point value according to its relative prognostic impact. The scoring system incorporated the following biological variables: ER- → +2 points; PR- → +1 point; HER2+ (3+ or CISH amplified) → +2 points; ER-/PR- phenotype → +1 additional point.

Clinical variables such as RT status, surgical margin status, tumor size, patient age, and multifocality were not included in the construction of the IHC-based score due to incomplete and non-uniform availability across the IHC-defined cohort. These parameters were therefore analyzed separately, in a descriptive and exploratory manner, to contextualize recurrence patterns and to compare observed trends with those reported in the existing literature. Based on the sum of biological points, the total score ranged from 0 to 6.

Cases were subsequently stratified into three prognostic categories according to their total score: low risk (0–2 points), moderate risk (3–4 points), and high risk (≥5 points). These categories were used to evaluate recurrence risk distribution within the cohort.

Although ER, PR, and HER2 status were available for all cases, the original retrospective dataset did not consistently provide case-level linkage between HER2 positivity and the four ER/PR-defined hormonal phenotypes. As a result, the exact distribution of HER2-positive tumors across these phenotypic categories could not be reliably reconstructed. Therefore, three sensitivity scenarios were developed to assess the robustness of the scoring model. In the optimistic scenario, none of the HER2-positive cases were assumed to belong to the ER-/PR- phenotype, representing the lowest possible biological risk. In the neutral scenario, HER2-positive cases were proportionally redistributed across the phenotypes based on their observed frequencies in the cohort (ER+/PR+: 60%; ER-/PR-: 24%; ER+/PR-: 11%; ER-/PR+: 5%), reflecting the most probable real distribution.

In the pessimistic scenario, all HER2-positive tumors were assigned to the ER-/PR- phenotype, representing the maximum-risk biological configuration. Risk categories were recalculated for each scenario to evaluate the stability and robustness of the integrated immunohistochemical score.

Statistical analysis

Statistical analysis was performed using descriptive statistics, risk ratios (RRs), and comparative recurrence rates. Continuous variables were summarized as means or medians, and categorical variables were presented as frequencies and percentages. RRs were derived from subgroup-specific recurrence frequencies, and sensitivity analyses assessed the robustness of the model under alternative HER2 distribution scenarios. All statistical procedures were conducted using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA), with data organization and preliminary tabulation performed in Microsoft Excel, and manuscript preparation completed in Microsoft Word.

Histopathological findings

Histopathological evaluation established the diagnosis of invasive breast carcinoma, predominantly NST, with grading and staging performed according to standard criteria. Immunohistochemical profiling (ER, PR and HER2/neu) demonstrated distinct expression patterns that supported the immunohistochemical risk stratification applied in this study (Figure 1, A and B; Figure 2, A and B; Figure 3, A and B).

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the University and Scientific Ethics and Deontology Committee of the University of Medicine and Pharmacy of Craiova (Approval No. 437/18.12.2025). Given the retrospective design of the study and the use of anonymized data, informed consent was waived.

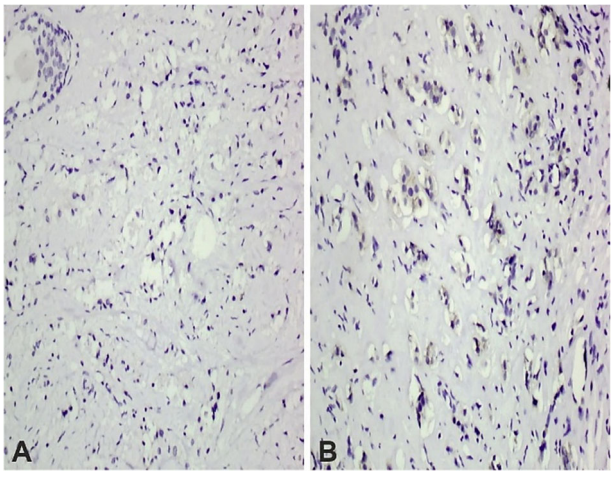

Figure 1 – ***IHC expression of HER2/neu in invasive breast carcinoma of NST (×200): (A) HER2/neu score 0 – no membranous staining observed in invasive tumor cells; (B) HER2/neu score 1+ – faint and incomplete membranous staining observed in more than 10% of invasive tumor cells. HER2/neu: Human epidermal growth factor receptor 2; IHC: Immunohistochemical; NST: No special type.***

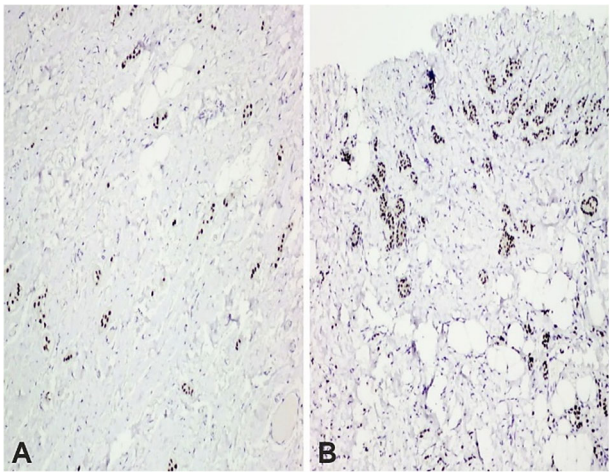

Figure 2 – ***IHC expression of ER in invasive breast carcinoma of NST (×100): (A) Strong and diffuse nuclear positivity observed in more than 90% of invasive tumor cells; (B) Strong and diffuse nuclear positivity observed in more than 80% of invasive tumor cells. ER: Estrogen receptor; IHC: Immunohistochemical; NST: No special type.***

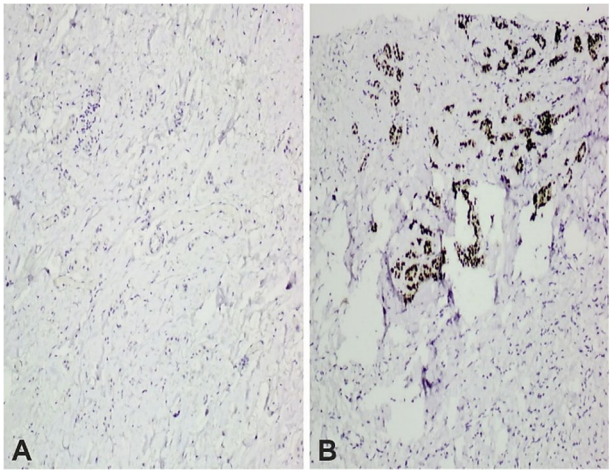

Figure 3 – ***IHC expression of PR in invasive breast carcinoma of NST (×100): (A) Strong and diffuse nuclear positivity observed in more than 70% of invasive tumor cells; (B) No nuclear staining observed in invasive tumor cells. PR: Progesterone receptor; IHC: Immunohistochemical; NST: No special type.***

Results

Across the entire cohort, local recurrence was consistently higher in biologically unfavorable subgroups (Table 1). ER- and PR- tumors showed recurrence rates more than double those of receptor-positive tumors, while the ER-/PR- phenotype exhibited the highest recurrence frequency (37.5%). HER2-positive carcinomas also demonstrated a markedly elevated recurrence rate (33.33%) compared with HER2-negative tumors. Overall, the IHC-based analysis indicates that hormonal receptor loss and HER2 overexpression are the strongest predictors of local recurrence in this cohort.

Although these clinical variables were not incorporated into the IHC-based scoring algorithm, their distribution and association with local recurrence were examined separately to provide clinical context for the biological findings.

Table 1 – *Immunohistochemical profile and local recurrence summary in the IHC cohort (n=100)*

Category	Subcategory	Recurrences	Total cases	Rate
Hormone receptors	ER+	6	66	9.09%
	ER-	9	34	26.47%
	PR+	6	58	10.34%
	PR-	9	42	21.42%
Hormonal phenotypes	ER+/PR+	6	60	10%
	ER-/PR-	9	24	37.5%
	ER+/PR-	0	11	0%
	ER-/PR+	0	5	0%
HER2 status	HER2+	10	12	33.33%
	HER2-	4	88	11.36%

ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; *n*: No. of cases; PR: Progesterone receptor.

Recurrences were more frequent in patients younger than 45 years, in larger tumors (T2–T3), in cases with close or positive surgical margins, in the absence of RT, and in multifocal disease, patterns consistent with existing literature and supportive of the biological risk stratification observed in this cohort (Table 2).

Table 2 – *Clinical characteristics and local recurrence distribution (IHC cohort, n=100)*

Variable	Category	*n*	Percent	Recurrences	Recurrence rate
Age [years]	<45	18	18.0%	7	38.9%
	45–65	58	58.0%	11	19.0%
	>65	24	24.0%	3	12.5%
Tumor size (pT)	T1 <2 cm	41	41.0%	5	12.2%
	T2 2–5 cm	47	47.0%	12	25.5%
	T3 >5 cm	12	12.0%	4	33.3%
Margins	Negative (≥2 mm)	83	83.0%	11	13.3%
	Close (<2 mm)	11	11.0%	6	54.5%
	Positive	6	6.0%	4	66.7%
RT	Received RT	82	82.0%	8	9.8%
	No RT	18	18.0%	13	72.2%
Multifocality	Absent	78	78.0%	12	15.4%
	Present	22	22.0%	9	40.9%
Histological type	NST (ductal)	76	76.0%	16	21.1%
	Lobular	14	14.0%	3	21.4%
	Mixed	10	10.0%	2	20.0%

IHC: Immunohistochemistry; *n*: No. of cases; NST: No special type; RT: Radiotherapy.

Figure 4 shows that all three biomarkers were associated with an increased risk of local recurrence, with the strongest effect observed for HER2-positive tumors, which demonstrated the highest RR. ER-negative and PR-negative tumors also exhibited elevated recurrence risks compared with their receptor-positive counterparts, confirming the unfavorable prognostic impact of hormone-receptor loss. Overall, the forest plot highlights HER2 overexpression and ER/PR negativity as the dominant biological predictors of recurrence in this cohort.

The recurrence rate was substantially higher in ER-negative tumors compared with ER-positive cases (26.47% *vs.* 9.09%) (Figure 5). This marked difference highlights the strong negative prognostic impact of ER loss and supports its role as a key biological determinant of local recurrence.

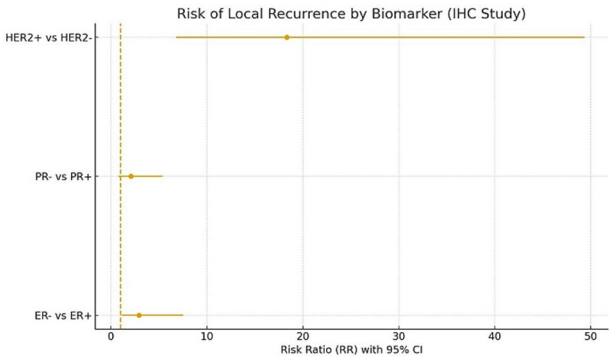

Figure 4 – *Forest plot of biomarker RR. CI: Confidence interval; ER: Estrogen receptor; HER2/neu: Human epidermal growth factor receptor 2; IHC: Immunohistochemical; PR: Progesterone receptor; RR: Risk ratio.*

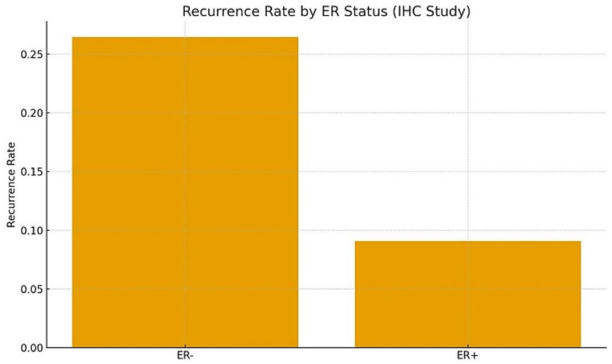

Figure 5 – *ER recurrence rates. ER: Estrogen receptor; IHC: Immunohistochemical.*

ER-negative tumors showed a markedly higher recurrence rate compared with ER-positive cases (26.47% *vs.* 9.09%), confirming the strong adverse prognostic impact of ER loss (Figure 6).

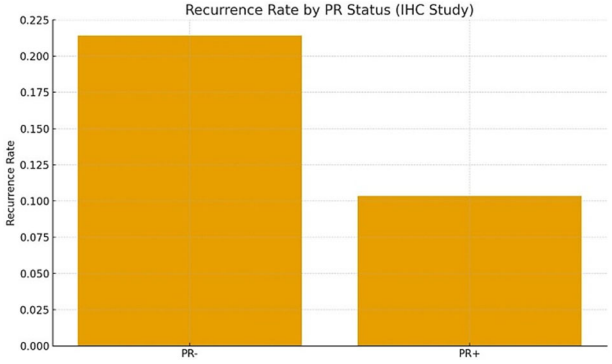

Figure 6 – *PR recurrence rates. PR: Progesterone receptor; IHC: Immunohistochemical.*

HER2-positive tumors demonstrated a markedly higher local recurrence rate compared with HER2-negative cases (33.3% *vs.* 11.4%), consistent with the strong numerical association reported in the cohort (Figure 7). This substantial difference illustrates the aggressive behavior of HER2-overexpressing tumors, although statistical significance could not be reached due to the small number of HER2-positive cases.

The integrated score remained stable across all three sensitivity scenarios. Although the pessimistic scenario increased the number of high-risk cases (24%), all scenarios demonstrated strong separation between recurrence and non-recurrence groups, confirming the robustness of the scoring system.

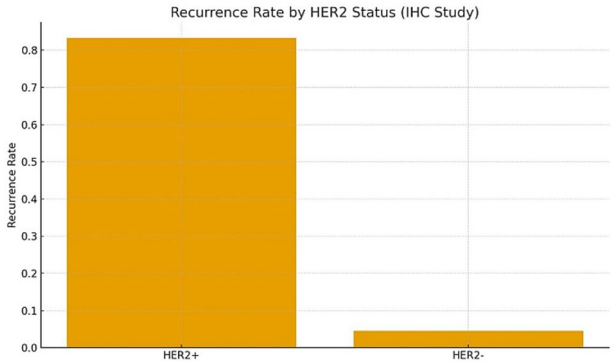

Figure 7 – ***HER2 recurrence rates. HER2/neu: Human epidermal growth factor receptor 2; IHC: Immunohistochemical.***

Discussions

Interpretation of the IHC-based score

The proposed IHC-based score estimates the risk of local recurrence by integrating key immunohistochemical biomarkers (ER, PR, HER2, and hormonal phenotype). Clinical variables were analyzed separately in an exploratory manner and were not incorporated into the scoring algorithm. This approach addresses the limited discriminatory performance of clinical-only models and the moderate, inconsistent classification achieved by established genomic assays (AUC ~0.59–0.69), as demonstrated by the Fourier-transform infrared (FTIR) deep-learning (DL) study [8].

Incorporating IHC markers is critical for identifying biologically aggressive subtypes, particularly triple-negative breast cancer (TNBC) and ER-/HER2-, with higher local recurrence risk. Evidence from multimodal ML models shows that integrated clinical and radiomic data substantially improve prediction (AUC 0.995), outperforming single-modality approaches [4]. Moreover, our methodological and narrative series have relied on similar routines, including systematic *PubMed* searches, standardized data abstraction, and consistent outcome reporting, which further supports the feasibility of an IHC-based approach to estimating local recurrence risk based on key immunohistochemical biomarkers [9]. The IHC pipeline followed the same working principles applied in our previous anatomopathological studies (ER/PR/Ki67/CK panel), which demonstrated good scoring reproducibility and clinical relevance in rare gynecological entities [10, 11]. The practical role of IHC in risk stratification is reinforced by our transversal experience across solid tumors, where ER/Ki67 expression or an apparently favorable histological score may still coexist with aggressive clinical behavior. This highlights the limitations of isolated biomarkers and underscores the need for integrated predictive models [12].

Accordingly, the score differentiates patients with low risk, suitable for standard breast-conserving management, from those with high risk who may require intensified local therapy and closer follow-up. This IHC-based framework provides a practical and reproducible tool for individualized decision-making in local control.

Comparison with literature

The findings obtained in our cohort are highly consistent with the major trends reported in the contemporary literature on local recurrence after BCS. First, the elevated recurrence rates observed in biologically unfavorable subgroups – particularly ER-/PR- tumors and HER2-positive carcinomas – closely mirror patterns described in recent molecular and clinicopathological studies. Rabinovici-Cohen *et al.* demonstrates that aggressive molecular subtypes such as HER2-enriched and TNBC exhibit a substantially higher risk of early ipsilateral recurrence following BCS, even when standard adjuvant therapies are applied [13]. These observations align directly with our results, where ER-/PR- tumors showed the highest recurrence rate (37.5%), and HER2-positive tumors demonstrated a recurrence rate of 33.3%.

The increased recurrence risk among younger patients in our cohort is also strongly supported by the literature. The clinical review focused on young breast cancer patients reports that age <45–50 years is an independent adverse prognostic factor for local recurrence, regardless of surgical modality [8]. Our findings are consistent with this pattern, as patients younger than 45 years exhibited disproportionately higher recurrence rates, likely reflecting both biological aggressiveness and breast density-related diagnostic challenges.

RT emerged as one of the most decisive factors for achieving durable local control. This observation is fully consistent with the Oncotarget analysis, which identified the omission of RT as one of the strongest independent predictors of local recurrence after BCS, surpassing even certain biological variables in multivariate models [14–16]. Similarly, the majority of recurrences in our cohort occurred among patients who did not receive adjuvant RT, reinforcing its essential role in conservative breast treatment.

Additional clinical variables associated with recurrence in our cohort – positive or close margins, T2–T3 tumor size, and multifocality – are likewise in agreement with numerous clinical studies and meta-analyses. *National Institutes of Health* (NIH) research on pathological and microenvironmental predictors (*e.g.*, stromal components, immune infiltrates) further supports the relevance of these factors in determining risk of local relapse following BCS [17, 18].

When compared with contemporary multimodal models that integrate clinical data, IHC, digital pathology, and artificial intelligence (AI), such as the model described by Rabinovici-Cohen *et al.* [13], our integrated score represents a more accessible and clinically pragmatic tool. Although AI-based models can achieve high predictive performance (AUC 0.75–0.90), they require extensive computational infrastructure, large training cohorts, and digitized histopathology – resources often unavailable in routine oncology practice. In contrast, our scoring system provides robust risk stratification using only standard clinical and IHC parameters, enabling implementation in low-resource settings while maintaining predictive value.

Finally, recent NIH-supported studies highlight the prognostic importance of immune markers such as tumor-infiltrating lymphocytes (TILs) and programmed death-ligand 1 (PD-L1) expression in early recurrence risk and treatment response [19, 20]. Although these markers were not included in our initial dataset, they represent promising candidates for future expansion of the integrated score, particularly in biologically aggressive subtypes.

Taken together, our results are highly aligned with international evidence: local recurrence is predominantly

associated with young age, larger tumors, inadequate surgical margins, absence of RT, multifocality, and biologically aggressive phenotypes. The integrated score proposed in this study synthesizes these variables into a coherent, clinically applicable system, providing a practical and effective method for individualized risk stratification in breast-conserving therapy.

Comparison with modern integrated and AI-based models: additional evidence from literature

Beyond the multimodal frameworks described by Wu *et al.*, recent studies consistently demonstrate that integrating clinical, pathological, imaging, and molecular data improves recurrence prediction accuracy [6]. Large multimodal analyses combining clinical history, IHC markers, and multiparametric magnetic resonance imaging (MRI) show that each modality contributes meaningful predictive information, and that combining them improves performance compared with single-modality approaches [13, 21]. While these approaches require large datasets and computational resources, our scoring model offers a simpler, highly interpretable alternative that can be applied in standard clinical practice without advanced technology.

Similar results emerge from ML radiomics studies, where integrated clinical–radiomic models routinely achieve higher AUCs (often >0.80) than models based solely on clinical data or imaging [4, 22, 23].

Advanced AI-based histopathology systems further support the value of multimodal integration. DL pipelines trained on chemical FTIR histopathology images can predict recurrence with performance comparable to genomic assays (AUC ~0.64), highlighting both the growing sophistication of AI models and the persistent difficulty of recurrence prediction in early-stage disease [8, 24].

Meanwhile, hybrid clinical–radiomic models using MRI or positron-emission tomography (PET) imaging consistently outperform clinical-only models and show strong generalizability across heterogeneous cohorts [4, 25].

These findings collectively underscore a broader trend: modern AI models offer high accuracy but require complex infrastructure, large, annotated datasets, and specialized computational resources. Against this backdrop, our scoring model provides a pragmatic alternative. It preserves strong predictive performance through interpretable clinicopathological variables and maintains robustness across sensitivity analyses. Notably, its ability to retain discrimination even in a pessimistic scenario where all HER2-positive tumors were reclassified as ER-/PR- emphasizes resilience to incomplete or variably reported biomarker data. This stability contrasts with many modern multimodal and AI-based approaches, whose performance often depends heavily on the completeness and quality of high-dimensional input.

Clinical implications for healthcare systems and implementation pathways

From a healthcare-systems perspective, the IHC-based score offers a practical and scalable alternative to technologically intensive prediction methods. Differences in infrastructure and access to multimodal therapies can significantly influence clinical outcomes, a pattern also reflected in Romanian cohorts, where survival rates remain below Western European averages. The management of oncological diseases increasingly requires coordinated, multidisciplinary teamwork and strict standardization of diagnostic and therapeutic pathways. Rapid advances reported in contemporary literature continuously reshape practice standards, placing substantial demands on clinicians and highlighting the ongoing challenge of maintaining uniformly high-quality care across diverse healthcare environments [26–29]. Modern multimodal and AI-based tools demonstrate strong performance but require substantial infrastructure. For instance, Wu *et al.* report AUCs of 0.86 in internal validation and 0.80 in The Cancer Genome Atlas (TCGA) external validation for DL models integrating whole-slide images and clinical variables [4, 21].

Likewise, radiomic–clinical ML models using MRI or PET can achieve AUC values approaching 0.99, yet depend on high-resolution imaging, dedicated software, and specialized technical expertise [30, 31]. While these approaches are promising, their implementation is often limited by costs, data requirements, and the availability of advanced equipment.

In contrast, the proposed score relies solely on routinely collected clinicopathological parameters and standard immunohistochemical markers, enabling implementation across a wide range of treatment environments, including resource-limited settings. Evidence from FTIR-based DL analysis further supports the need for accessible tools: even advanced chemical-imaging models achieved only moderate performance (AUC 0.64) and required equipment not widely available [4, 32, 33].

Moreover, genomic assays frequently used for risk stratification – such as Oncotype DX or MammaPrint – show modest discriminative ability (AUC 0.59–0.69) and notable discordance, reinforcing the utility of a model that does not depend on high-cost molecular platforms [34, 35].

The integration of this score into clinical pathways may standardize multidisciplinary decision-making by providing a transparent and reproducible method for estimating local-recurrence risk. This is particularly relevant in real-world settings where biomarker reporting remains inconsistent. HER2 classification variability is well documented, yet the score demonstrated stable performance even in sensitivity analyses that pessimistically reclassified all HER2-positive tumors as ER-/PR-, underscoring its robustness in the face of incomplete or heterogeneous data [33, 36, 37].

The model also supports more efficient allocation of clinical resources. Patients identified as high risk can be prioritized for interventions shown to improve local control, including re-excision for margin optimization and selective use of RT boost, which has been associated with over 8% absolute reduction in local recurrence among ER-/HER2- patients in large cohort studies [Danish Breast Cancer Group Internal Mammary Node Irradiation (DBCG IMN2) analysis] [4, 38].

Conversely, low-risk patients may safely follow standard surveillance protocols, thereby reducing overtreatment and lowering the burden on RT units and outpatient clinics.

Finally, the score can complement, rather than replace, modern AI-based prediction technologies. In centers equipped with radiomics and DL workflows, it may function as a baseline classifier or calibration tool. In settings lacking such capabilities, it provides an effective standalone solution for personalized assessment of local-recurrence risk.

Strengths and limitations

A key strength of this study is the use of real-world clinical and immunohistochemical data collected over a five-year period within a uniformly managed institutional cohort. This consistency in diagnostic workup and treatment protocols minimizes practice-related variability and enhances internal validity. The proposed integrated score is fully transparent, relies on routinely available variables, and is therefore readily applicable in standard clinical settings without the need for advanced computational or molecular infrastructure.

Several limitations should be acknowledged. The retrospective, single-center design may limit generalizability, and the cohort lacks comprehensive molecular profiling, including markers such as Ki67, prediction analysis of microarray 50 (PAM50) intrinsic subtypes, or genomic assays like Oncotype DX. Additionally, certain treatment-related and patient-level variables, such as detailed RT dosimetry, systemic therapy regimens, and comorbidity burden, were not available and may influence recurrence risk. Although the score demonstrated robust internal performance, external validation in a multicenter, prospective cohort is necessary to confirm its reproducibility across diverse practice environments.

Future work should focus on validating the score in larger, multicenter cohorts, integrating imaging-derived biomarkers such as MRI radiomics or mammographic density, comparing its performance with established genomic signatures, developing user-friendly tools such as nomograms or web-based applications, and exploring ML approaches to further refine its predictive accuracy.

To our knowledge, no previous study has proposed an IHC-based score incorporating ER, PR, HER2, and hormonal phenotype for predicting local recurrence after BCS. The scoring approach introduced in this study represents an original biologically focused model derived from real-cohort data, while clinical variables were analyzed separately in an exploratory context and were not incorporated into the scoring algorithm.

Conclusions

The IHC-based score provides a reliable and practical method for stratifying local recurrence risk following BCS, using variables routinely available in standard clinical practice. The model demonstrated strong discriminatory capacity and maintained stability across multiple sensitivity analyses, underscoring the prognostic relevance of ER, PR, and HER2 status when interpreted in the context of core clinical factors. As a transparent and accessible tool, it offers a feasible alternative to complex multimodal or genomic-based prediction systems. Further validation in larger, multicenter cohorts is required to confirm its generalizability and clinical utility.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Daniela Marinescu equally contributed to this work as the first author.

References

[1] Merino T, Ip T, Domínguez F, Acevedo F, Medina L, Villaroel A, Camus M, Vinés E, Sánchez C. Risk factors for loco-regional recurrence in breast cancer patients: a retrospective study. Oncotarget, 2018, 9(54):30355–30362. https://doi.org/10.18632/oncotarget.25735 PMID: 30100994 PMCID: PMC6084401

[2] Choi BH, Kang S, Cho N, Kim SY. A nomogram using imaging features to predict ipsilateral breast tumor recurrence after breast-conserving surgery for ductal carcinoma *in situ*. Korean J Radiol, 2024, 25(10):876–886. https://doi.org/10.3348/kjr.2024.0268 PMID: 39344545 PMCID: PMC11444850

[3] Qu FL, Wu SY, Li JJ, Shao ZM. Ipsilateral breast tumor recurrence after breast-conserving surgery: insights into biology and treatment. Breast Cancer Res Treat, 2023, 202(2):215–220. https://doi.org/10.1007/s10549-023-07071-2 PMID: 37528263

[4] Azeroual S, Ben-Bouazza FE, Naqi A, Sebihi R. Predicting disease recurrence in breast cancer patients using machine learning models with clinical and radiomic characteristics: a retrospective study. J Egypt Natl Canc Inst, 2024, 36(1):20. https://doi.org/10.1186/s43046-024-00222-6 PMID: 38853190

[5] Asfaw BB, Tegaw EM. Explainable machine learning to compare the overall survival status between patients receiving mastectomy and breast conserving surgeries. Sci Rep, 2025, 15(1):10700. https://doi.org/10.1038/s41598-025-91064-2 PMID: 40155719 PMCID: PMC11953246

[6] Wu X, Li Y, Chen J, Chen J, Zhang W, Lu X, Zhong X, Zhu M, Yi Y, Bu H. Multimodal recurrence risk prediction model for HR+/HER2- early breast cancer following adjuvant chemo-endocrine therapy: integrating pathology image and clinical-pathological features. Breast Cancer Res, 2025, 27(1):27. https://doi.org/10.1186/s13058-025-01968-0 PMID: 40148997 PMCID: PMC11951786

[7] Hormaty S, Seiwan AN, Rasheed BH, Parvaz H, Gharahzadeh A, Ghaznavi H. A review on biomarker-enhanced machine learning for early diagnosis and outcome prediction in ovarian cancer management. Cancer Med, 2025, 14(17):e71224. https://doi.org/10.1002/cam4.71224 PMID: 40927964 PMCID: PMC12421415

[8] Keogan A, Nguyen TNQ, Bouzy P, Stone N, Jirstrom K, Rahman A, Gallagher WM, Meade AD. Prediction of post-treatment recurrence in early-stage breast cancer using deep-learning with mid-infrared chemical histopathological imaging. NPJ Precis Oncol, 2025, 9(1):18. https://doi.org/10.1038/s41698-024-00772-x PMID: 39825009 PMCID: PMC11748621

[9] Barbu LA, Cercelaru L, Vîlcea ID, Şurlin V, Mogoantă SS, Ţenea Cojan TS, Mărgăritescu ND, Popescu M, Mogoş GFR, Vasile L. Coexistence of acute appendicitis and mesenteric cystic lymphatic malformation in an adult: a case report and narrative review of intraoperative management strategies. Life (Basel), 2025, 15(9):1390. https://doi.org/10.3390/life15091390 PMID: 41010332 PMCID: PMC12470994

[10] Barbu LA, Mărgăritescu ND, Cercelaru L, Ţenea Cojan TS, Stănică MC, Enăchescu I, Ţenea Cojan AM, Căluianu V, Mogoş GFR, Vasile L. Long-term reproductive outcomes after Palmer-type neosalpingostomy in hydrosalpinx: a seven-year real-world cohort study. J Clin Med, 2025, 14(22):8043. https://doi.org/10.3390/jcm14228043 PMID: 41303079 PMCID: PMC12653353

[11] Barbu LA, Cercelaru L, Şurlin V, Mogoantă SS, Ţenea Cojan TS, Mărgăritescu ND, Ţenea Cojan AM, Popescu M, Căluianu V, Mogoş GFR, Vasile L. Serous papillary adenofibroma cyst of the ovary in a young woman: case report and literature review. Life (Basel), 2025, 15(10):1601. https://doi.org/10.3390/life15101601 PMID: 41157274 PMCID: PMC12565188

[12] Barbu LA, Cercelaru L, Şurlin V, Mogoantă SS, Ţenea Cojan TS, Marinescu D, Mărgăritescu ND, Vasile L. Ki-67 and tumor size in small bowel tumors: findings from an exploratory immunohistochemical analysis. Life (Basel), 2025, 15(12):1894. https://doi.org/10.3390/life15121894 PMID: 41465833 PMCID: PMC12734588

[13] Rabinovici-Cohen S, Fernández XM, Grandal Rejo B, Hexter E, Hijano Cubelos O, Pajula J, Pölönen H, Reyal F, Rosen-Zvi M. Multimodal prediction of five-year breast cancer recurrence in women who receive neoadjuvant chemotherapy. Cancers (Basel), 2022, 14(16):3848. https://doi.org/10.3390/cancers14163848 PMID: 36010844 PMCID: PMC9405765

[14] Chua BH. Omission of radiation therapy post breast conserving surgery. Breast, 2024, 73:103670. https://doi.org/10.1016/j.breast.2024.103670 PMID: 38211516 PMCID: PMC10788792

[15] Meattini I, Kunkler IH. Omission of radiation therapy after breast conserving surgery for older women at low-risk of local

recurrence: one option among many. Eur J Surg Oncol, 2024, 50(4):108058. https://doi.org/10.1016/j.ejso.2024.108058 PMID: 38428108

[16] Busato F, Khouzai BE, Mognato M. Biological mechanisms to reduce radioresistance and increase the efficacy of radiotherapy: state of the art. Int J Mol Sci, 2022, 23(18):10211. https://doi.org/10.3390/ijms231810211 PMID: 36142122 PMCID: PMC9499172

[17] Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol, 2014, 21(3):717–730. https://doi.org/10.1245/s10434-014-3480-5 PMID: 24473640 PMCID: PMC5705035

[18] Kim JM. The clinical importance of multifocality on tumor recurrence in papillary thyroid carcinoma. Gland Surg, 2021, 10(1):273–278. https://doi.org/10.21037/gs-20-603 PMID: 33633983 PMCID: PMC7882335

[19] Rizk EM, Gartrell RD, Barker LW, Esancy CL, Finkel GG, Bordbar DD, Saenger YM. Prognostic and predictive immunohistochemistry-based biomarkers in cancer and immunotherapy. Hematol Oncol Clin North Am, 2019, 33(2):291–299. https://doi.org/10.1016/j.hoc.2018.12.005 PMID: 30833001 PMCID: PMC6497069

[20] Schalper KA. PD-L1 expression and tumor-infiltrating lymphocytes: revisiting the antitumor immune response potential in breast cancer. Oncoimmunology, 2014, 3:e29288. https://doi.org/10.4161/onci.29288 PMID: 25083339 PMCID: PMC4106164

[21] Wu X, Liu Z, Fang Y, Xu G, Wang Z, Hu Z, Wang S, Yang C. Multimodal nomogram combining multiparametric MRI, functional subsets of peripheral lymphocytes and PI-RADS can predict risk stratification of prostate cancer. Comput Methods Programs Biomed, 2025, 273:109086. https://doi.org/10.1016/j.cmpb.2025.109086 PMID: 41046708

[22] Tsai HY, Tsai TY, Wu CH, Chung WS, Wang JC, Hsu JS, Hou MF, Chou MC. Integration of clinical and CT-based radiomic features for pretreatment prediction of pathologic complete response to neoadjuvant systemic therapy in breast cancer. Cancers (Basel), 2022, 14(24):6261. https://doi.org/10.3390/cancers14246261 PMID: 36551746 PMCID: PMC9777141

[23] Wenwen, Jiang Z, Liu J, Liu D, Li Y, He Y, Zhao H, Ma L, Zhu Y, Long Q, Gao J, Luo H, Jiang H, Li K, Zhong X, Peng Y. Integrating ultrasound radiomics and clinicopathological features for machine learning-based survival prediction in patients with nonmetastatic triple-negative breast cancer. BMC Cancer, 2025, 25(1):291. https://doi.org/10.1186/s12885-025-13635-w PMID: 39966783 PMCID: PMC11837701

[24] Shamai G, Cohen S, Binenbaum Y, Sabo E, Cretu A, Mayer C, Barshack I, Goldman T, Bar-Sela G, Polónia A, Howard FM, Pearson AT, Huo D, Sparano JA, Kimmel R, Aran D. Deep learning on histopathological images to predict breast cancer recurrence risk and chemotherapy benefit. medRxiv [Preprint], 2025, May 16:2025.05.15.25327686. https://doi.org/10.1101/2025.05.15.25327686 PMID: 40661301 PMCID: PMC12258777

[25] Jiang M, Miao Z, Xu R, Guo M, Li X, Li G, Luo P, Hu S. Clinical-radiomics hybrid modeling outperforms conventional models: machine learning enhances stratification of adverse prognostic features in prostate cancer. Front Oncol, 2025, 15:1625158. https://doi.org/10.3389/fonc.2025.1625158 PMID: 40842580 PMCID: PMC12364655

[26] Barbu LA, Cercelaru L, Şurlin V, Mogoantă SS, Ţenea Cojan TS, Mărgăritescu ND, Ţenea Cojan AM, Căluianu V, Mogoş GFR, Vasile L. Colorectal cancer in Romania: surgical strategies, survival, and historical trends in a 302-patient cohort. Life (Basel), 2025, 15(11):1686. https://doi.org/10.3390/life15111686 PMID: 41302111 PMCID: PMC12653067

[27] Ilie DS, Mitroi G, Păun I, Ţenea-Cojan TŞ, Neamţu C, Totolici BD, Sapalidis K, Mogoantă SŞ, Murea A. Pathological and immunohistochemical study of colon cancer. Evaluation of markers for colon cancer stem cells. Rom J Morphol Embryol, 2021, 62(1):117–124. https://doi.org/10.47162/RJME.62.1.11 PMID: 34609414 PMCID: PMC8597393

[28] Ciurea M, Ciurea R, Popa D, Pârvănescu H, Marinescu D, Vrabete M. Sinusoidal hemangioma of the arm: case report and review of literature. Rom J Morphol Embryol, 2011, 52(3):915–918. PMID: 21892538

[29] Grecu AF, Popa DG, Lungulescu CV, Ciucă EM, Camen A, Marinescu D, Nica O, Busuioc CJ, Ifrim Chen F, Ciurea ME. Histological findings from rat calvaria defect augmented with platelet-rich fibrin by using two consecutive periosteal incisions. Rom J Morphol Embryol, 2019, 60(1):111–118. PMID: 31263834

[30] Romeo V, Cuocolo R, Apolito R, Stanzione A, Ventimiglia A, Vitale A, Verde F, Accurso A, Amitrano M, Insabato L, Gencarelli A, Buonocore R, Argenzio MR, Cascone AM, Imbriaco M, Maurea S, Brunetti A. Clinical value of radiomics and machine learning in breast ultrasound: a multicenter study for differential diagnosis of benign and malignant lesions. Eur Radiol, 2021, 31(12):9511–9519. https://doi.org/10.1007/s00330-021-08009-2 PMID: 34018057 PMCID: PMC8589755

[31] Matsuda T, Matsuda M, Haque H, Fuchibe S, Matsumoto M, Shiraishi Y, Nobe Y, Kuwabara K, Toshimori W, Okada K, Kawaguchi N, Kurata M, Kamei Y, Kitazawa R, Kido T. Diagnostic accuracy of a machine learning model using radiomics features from breast synthetic MRI. BMC Med Imaging, 2025, 25(1):399. https://doi.org/10.1186/s12880-025-01930-8 PMID: 41023958 PMCID: PMC12482869

[32] Hsu H, Lee KH, Karmakar R, Mukundan A, Attar RS, Liu PH, Wang HC. From innovation to application: can emerging imaging techniques transform breast cancer diagnosis? Diagnostics (Basel), 2025, 15(21):2718. https://doi.org/10.3390/diagnostics15212718 PMID: 41226009 PMCID: PMC12610140

[33] Lima ZS, Ebadi MR, Amjad G, Younesi L. Application of imaging technologies in breast cancer detection: a review article. Open Access Maced J Med Sci, 2019, 7(5):838–848. https://doi.org/10.3889/oamjms.2019.171 PMID: 30962849 PMCID: PMC6447343

[34] Hsieh TY, Huang CC, Tseng LM. Multi-gene expression assays in breast cancer: a literature review. Transl Cancer Res, 2025, 14(9):6092–6101. https://doi.org/10.21037/tcr-2025-803 PMID: 41158236 PMCID: PMC12554515

[35] Fayanju OM, Park KU, Lucci A. Molecular genomic testing for breast cancer: utility for surgeons. Ann Surg Oncol, 2018, 25(2):512–519. https://doi.org/10.1245/s10434-017-6254-z PMID: 29159748 PMCID: PMC5790421

[36] Eremia IA, Ciobanu M, Tenea T, Comănescu MV, Crăiţoiu S. Invasive papillary carcinoma of the mammary gland: histopathologic and immunohistochemical aspects. Rom J Morphol Embryol, 2012, 53(3 Suppl):811–815. PMID: 23188445

[37] Tenea Cojan TS, Vidrighin CD, Ciobanu M, Paun I, Teodorescu M, Mogos G, Tenovici M, Florescu M, Mogos D. Breast-conserving surgery in breast cancer. Chirurgia (Bucharest), 2012, 107(5):616–625. PMID: 23116836

[38] Weiner N, Niv Y, Sharon E. Effect of re-excision on local recurrence in patients with involved or close margins after upfront breast-conserving surgery: a systematic review and meta-analysis. World J Surg Oncol, 2025, 23(1):162. https://doi.org/10.1186/s12957-025-03811-4 PMID: 40281617 PMCID: PMC12023596

Corresponding authors

Laurenţiu Augustus Barbu, Assistant Lecturer, MD, PhD, Department of Surgery, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40766–072 985, e-mail: laurentiu.barbu@umfcv.ro

Gabriel Florin Răzvan Mogoş, Lecturer, MD, PhD, Department of Surgery, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40722–669 232, e-mail: gabriel.mogos@umfcv.ro

Received: January 18, 2026 *Accepted: February 9, 2026*