Breast Cancer: Targets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Prognostic Value of Ki-67 and Progesterone Receptor for Risk Stratification and Outcomes by Adjuvant Chemotherapy in Early Luminal-Type Breast Cancer

Hung-Hsun Chen[1,*], Shu-Jyuan Chang[2,*], Jung-Yu Kan[1], Fang-Ming Chen[1,3], Chung-Liang Li[1,3], Hidenobu Takahashi[1,3], Shen-Liang Shih[1,3], Ming-Feng Hou[1,3,4], Mei-Ren Pan[2,4], Ping-Fu Yang[1,3,*], Chi-Wen Luo[1,5]

[1]Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Graduate Institute of Clinical Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Gangshan Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [4]Drug Development and Value Creation Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan; [5]Department of Cosmetic Science and Institute of Cosmetic Science, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

*These authors contributed equally to this work

Correspondence: Ping-Fu Yang; Chi-Wen Luo, Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, Tel +886-7-3121101ext 6235; +886-7-3121101ext 2260, Fax +886-7-3165011, Email adiemus.0615@gmail.com; cwlo0623@gmail.com

Purpose: Risk stratification of hormone receptor–positive (HR+)/HER2-negative early breast cancer remains variable across studies. We aimed to develop and validate an immunohistochemistry (IHC)-based stratification framework (PR10/Ki20) and a quantitative risk score (RS), and to explore clinical outcomes according to receipt of adjuvant chemotherapy (CT).

Methods: This retrospective study analyzed a discovery cohort (KMTTH, n = 2633) and an external validation cohort (KMUH, n = 1147). Using prespecified cutoffs, patients were categorized into four groups: low risk (LR; PR ≥ 10% and Ki-67 < 20%), moderate risk 1 (MR1; PR < 10% and Ki-67 < 20%), moderate risk 2 (MR2; PR ≥ 10% and Ki-67 ≥ 20%), and high risk (HiR; PR < 10% and Ki-67 ≥ 20%). A quantitative *RS* was derived incorporating PR10/Ki20 categories, age, pathological T stage, and lymphovascular invasion.

Results: The PR10/Ki20 model demonstrated consistent prognostic performance across cohorts. HiR patients had significantly poorer disease-free survival (DFS) and overall survival (OS), whereas the LR group exhibited favorable outcomes. In the validation cohort, adjuvant CT was associated with improved DFS in the HiR group, whereas no statistically significant association was observed in the LR group. The *RS* separated patients into high- and low-*RS* groups with significantly different DFS in both cohorts (KMTTH: P = 0.005; KMUH: P = 0.004).

Conclusion: The PR10/Ki20 framework and the derived *RS* provide reproducible prognostic stratification in HR+/HER2− early breast cancer across two cohorts. In this retrospective analysis, CT use was associated with improved DFS among patients classified as high risk, while no statistically significant association was observed in the low-risk group. These findings may help inform risk-adapted discussions and generate hypotheses for prospective validation regarding treatment selection.

Keywords: breast cancer, PR, Ki-67, chemotherapy, risk stratification

Introduction

Breast cancer is a clinically heterogeneous disease characterized by diverse histopathological and molecular subtypes, each exhibiting distinct biological behaviors and clinical outcomes. Gene expression profiling has traditionally classified the disease into four major intrinsic subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and basal-like. These subtypes differ significantly in molecular characteristics, therapeutic responses, and

https://doi.org/10.2147/BCTT.S597707
Received: 1 February 2026
Accepted: 25 March 2026
Published: 1 April 2026

prognosis.[1,2] In routine clinical practice, immunohistochemistry (IHC) serves as a practical alternative for classification. Luminal tumors, defined by hormone receptor-positive (HR+) and HER2-negative (HER2-) status, constitute most breast cancer cases and generally carry a favorable prognosis.[3,4] However, within this group, luminal B tumors display increased proliferative activity and shorter survival rates compared to luminal A tumors, highlighting the need for accessible markers to guide risk-adapted management strategies.[5,6]

In early-stage luminal breast cancer, a central clinical question is how to select patients for adjuvant chemotherapy (CT) to maximize benefit while minimizing overtreatment. Although current guidelines often recommend CT to reduce recurrence risk, the absolute survival benefit is modest for many node-negative, HR+ patients.[7,8] Consequently, a substantial proportion of patients may be exposed to cytotoxic therapy and its adverse effects without meaningful clinical gain. The toxicity and long-term sequelae of CT underscore the need for robust and widely available markers to better stratify risk and spare low-risk individuals from unnecessary treatment.[9,10] Multigene assays such as Oncotype DX and MammaPrint are increasingly used to refine recurrence risk and inform chemotherapy decisions in early-stage HR+/HER2− breast cancer.[11] However, access, cost, and turnaround time remain barriers in many real-world settings.[12] Accordingly, an IHC-based framework using routinely reported biomarkers may serve as a pragmatic triage approach to identify clearly low- or high-risk cases and to prioritize genomic testing for patients in whom treatment decisions remain uncertain.

Among existing biomarkers, the nuclear proliferation marker Ki-67 and progesterone receptor (PR) expression are cornerstone tools for prognostic stratification in HR+/HER2- breast cancer.[13] However, their optimal cutoff values remain debated. The 2011 St. Gallen International Consensus initially recommended a Ki-67 threshold of <14% to define low proliferative activity and distinguish luminal A from luminal B tumors. Nevertheless, due to inter-laboratory variability, this cutoff showed limited reproducibility and risked overclassification.[14] To enhance clinical applicability, the 2013 St. Gallen Expert Panel revised the threshold to ≥20% to identify higher-risk disease.[15,16] Regarding PR expression, the ASCO/CAP guidelines define clinical positivity as nuclear staining ≥1%.[17] In contrast, a higher threshold of 20% is frequently used for molecular subtyping, where PR <20% serves as a surrogate marker for the more aggressive luminal B phenotype.[18,19] This dual-threshold framework highlights the need for refined IHC-based strategies to support clinically meaningful risk stratification.

Biologically, reduced PR expression is often interpreted as a surrogate of attenuated estrogen receptor (ER) signaling and has been associated with endocrine resistance and more aggressive tumor behavior.[20] In contrast, elevated Ki-67 reflects increased proliferative activity, a hallmark of luminal B like biology. Therefore, low PR combined with high Ki-67 may capture both reduced endocrine signaling and heightened proliferation, a pattern associated with poorer outcomes.[21,22] To address the ambiguity surrounding intermediate expression levels, this study adopted a stringent approach using prespecified, clinically informed cutoffs. We implemented a Ki-67 threshold of ≥20% in alignment with the 2013 St. Gallen revision,[15] evaluated in conjunction with a PR cutoff of <10%, which has been associated with impaired estrogen signaling and more aggressive tumor biology.[23,24] By requiring the concomitant presence of both PR <10% and Ki-67 ≥20%, our study proposes a robust binary stratification. This integrated signature provides a practical framework for risk stratification and for identifying patient subgroups with differential outcomes associated with adjuvant CT.

Materials and Methods

Study Population

This large-scale retrospective study analyzed data from two independent clinical centers. The discovery cohort comprised 2633 patients from Kaohsiung Municipal Ta-Tung Hospital (KMTTH), while the external validation cohort included 1147 patients from Kaohsiung Medical University Hospital (KMUH) to assess the reproducibility of findings. This study protocol was approved by the Institutional Review Board of KMUH (KMUHIRB-E(I)-20250170), which covered data collection at both participating centers. Informed consent was waived by the Institutional Review Board of KMUH because this was a retrospective study using de-identified data and posed minimal risk to participants. The study was conducted in accordance with the Declaration of Helsinki. We enrolled female patients with pathological T stage (pT1b–pT2), N0–1, and M0 breast cancer. Eligibility was limited to the luminal subtype, defined as ER-positive (>1%) and HER2- (IHC 0, 1+, or 2+

with negative in situ hybridization) according to ASCO/CAP guidelines. All patients underwent definitive surgery followed by standard adjuvant endocrine therapy.

Assessment of PR and Ki-67 Expression

PR and Ki-67 expression were obtained from routine clinical pathology reports based on immunohistochemistry (IHC) performed on formalin-fixed, paraffin-embedded (FFPE) tumor sections. IHC staining and reporting followed standardized institutional protocols at both centers. PR was reported as the percentage of tumor cell nuclei showing positive staining. Ki-67 was reported as the percentage of positively stained tumor nuclei assessed in hotspot areas, with at least 500 invasive tumor cells counted per case, consistent with routine clinical reporting practice.

IHC-Based Risk Stratification (PR10/Ki20 Model)

Risk stratification was performed using prespecified cutoffs of PR 10% and Ki-67 20% (PR10/Ki20). Patients were categorized into four mutually exclusive subgroups: low risk (LR; PR $\geq$ 10% and Ki-67 < 20%), moderate risk 1 (MR1; PR < 10% and Ki-67 < 20%), moderate risk 2 (MR2; PR $\geq$ 10% and Ki-67 $\geq$ 20%), and high risk (HiR; PR < 10% and Ki-67 $\geq$ 20%).

Construction of the Quantitative Risk Score (RS)

A quantitative *RS* was derived from the discovery cohort (KMTTH) using regression coefficients (β-values) from a multivariable Cox proportional hazards model. The β-values were the natural logarithms of the adjusted hazard ratios ($\beta = \ln(aHR)$) estimated from the multivariable model for each independent prognostic variable. The final model incorporated PR10/Ki20 categories, age, pathological T stage (pT), and lymphovascular invasion (LVI). Patients were subsequently stratified into low-*RS* and high-*RS* groups using the cohort-specific median *RS* as the cutoff.

Statistical Analysis

The primary endpoints were disease-free survival (DFS) and overall survival (OS). Survival curves were estimated using the Kaplan–Meier method and compared via the Log rank test. Variables were screened using univariable Cox regression; significant factors were entered into multivariable Cox models to determine independent predictors and calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). Multivariable models were adjusted for potential confounders, including age, pT stage, and LVI. Forest plots were generated to visualize hazard ratios and the association of adjuvant CT across risk strata. All statistical analyses were performed using SAS version 9.4 and R version 4.4.1. All tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

Patient Classification and Risk Distribution

Using PR expression and the Ki-67 index, we established a four-tier risk stratification model (PR10/Ki20) in the discovery cohort (KMTTH, n = 2633) and evaluated reproducibility in an external validation cohort (KMUH, n = 1147). Using prespecified cutoffs of PR 10% and Ki-67 20%, patients were categorized into four mutually exclusive subgroups (Figure 1A and B): LR (PR $\geq$ 10% and Ki-67 < 20%), MR1 (PR < 10% and Ki-67 < 20%), MR2 (PR $\geq$ 10% and Ki-67 $\geq$ 20%), and HiR (PR < 10% and Ki-67 $\geq$ 20%). Risk-group distributions were highly consistent between cohorts (Figure 1C). In the KMTTH cohort, LR comprised 56.4% of patients, followed by MR2 (22.0%), MR1 (13.5%), and HiR (8.1%). A comparable distribution was observed in the KMUH cohort: LR 54.5%, MR2 20.9%, MR1 15.6%, and HiR 9.0%. This concordance supports reproducibility of the PR10/Ki20 framework.

Consistency of Clinicopathological Characteristics

Baseline clinicopathological characteristics are summarized in Table 1. Both cohorts comprised patients with early-stage disease and showed broadly comparable profiles, including predominance of low histological grade (I/II), pT1 tumors, and node-negative status. Treatment patterns were similarly aligned: all patients underwent surgery, and approximately

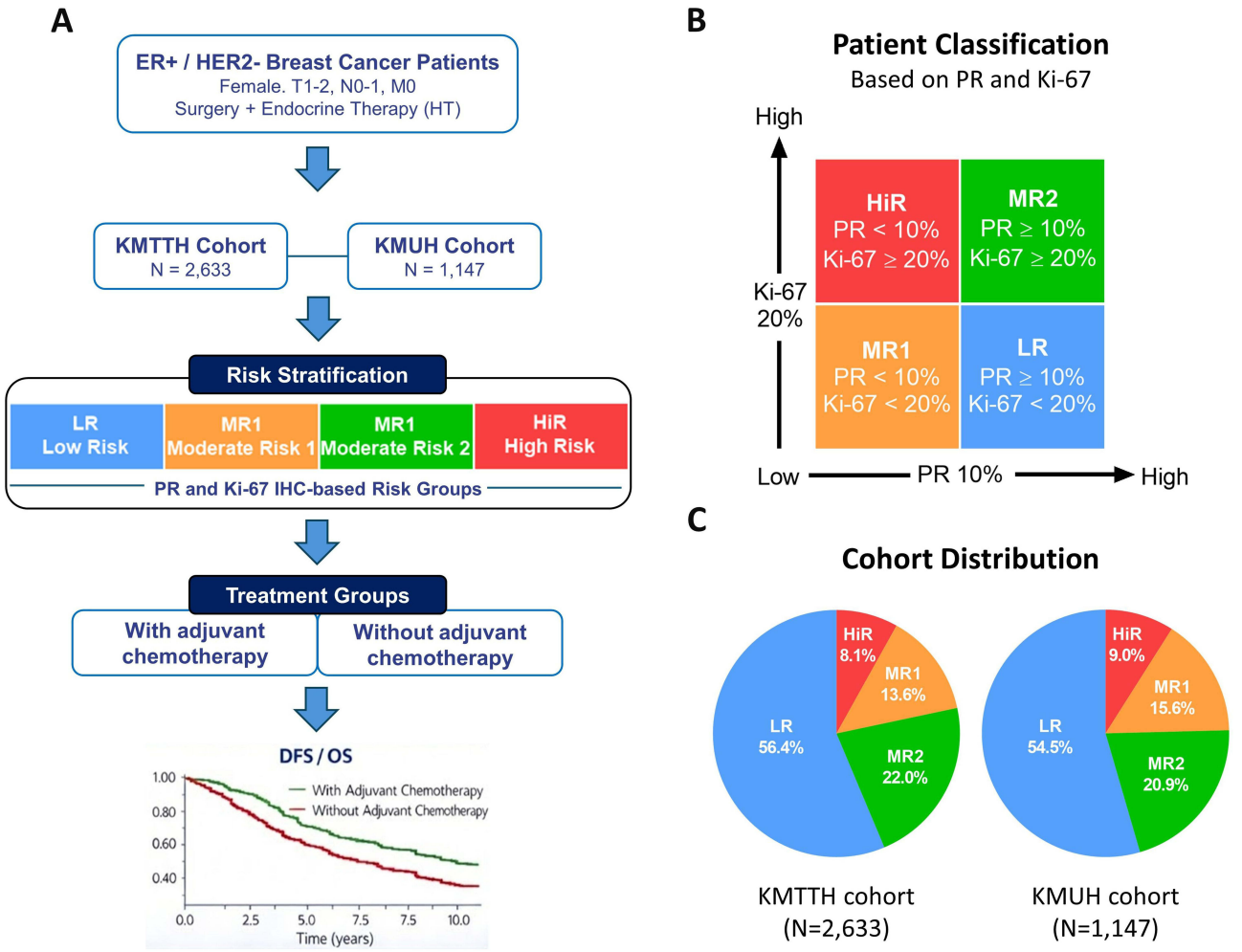

Figure 1 Study workflow and immunohistochemistry (IHC)-based risk stratification for ER+/HER2− early breast cancer. (**A**) Schematic overview of the study design. Patients with ER+/HER2− early breast cancer (pT1–2, N0–1, M0) were enrolled from the KMTTH (discovery) and KMUH (validation) cohorts to evaluate the prognostic performance of the PR10/Ki20 stratification model and clinical outcomes according to adjuvant chemotherapy (CT) receipt for disease-free survival (DFS) and overall survival (OS). (**B**) Classification matrix defining four mutually exclusive risk groups based on PR and Ki-67 thresholds: Low Risk (LR; PR ≥ 10%, Ki-67 < 20%), Moderate Risk 1 (MR1; PR < 10%, Ki-67 < 20%), Moderate Risk 2 (MR2; PR ≥ 10%, Ki-67 ≥ 20%), and High Risk (HiR; PR < 10%, Ki-67 ≥ 20%). (**C**) Distribution of the four risk groups within the KMTTH (n = 2633) and KMUH (n = 1147) cohorts.

one-third received adjuvant CT. Biomarker-defined risk groups also showed similar distributions across cohorts, with LR remaining the most prevalent subgroup, followed by MR2, MR1, and HiR. Collectively, these findings support the robustness of the model across independent datasets.

Prognostic Performance of the PR10/Ki20 Model

The PR10/Ki20 model demonstrated consistent prognostic performance. In the KMTTH cohort, the model separated patients into four groups with significantly different DFS and OS (both $P < 0.001$; Figure 2A). Pairwise comparisons confirmed that the HiR group had the poorest outcomes (DFS, $P = 0.002$; OS, $P < 0.001$; Figure 2B), whereas the LR group exhibited the most favorable prognosis (DFS, $P < 0.001$; OS, $P = 0.043$; Figure 2C). These findings were externally validated in the KMUH cohort. Kaplan-Meier analyses demonstrated clear survival separation across the four PR10/Ki20 groups (Figure 3A). The HiR group again demonstrated significantly worse survival (DFS, $P = 0.001$; OS, $P = 0.047$; Figure 3B). The LR group showed numerically better DFS ($P = 0.072$) without a significant OS difference ($P = 0.276$; Figure 3C).

Table 1 Patients Baseline Characteristics of Two Cohorts

Variable	KMTTH (n=2633)	KMUH (n=1147)
Age (years)		
Mean (range)	54(19–89)	55(25–87)
Follow-up time (months)		
Mean (range)	35.33(0.46–112.36)	23.73(0.66–71.84)
Histological Grade		
I/II	2241(86.36)	940(83.63)
III/IV	354(13.64)	184(16.37)
Tumor size		
T1	1761(66.88)	789(68.79)
T2	872(33.12)	358(31.21)
Lymph node		
N0	2041(77.69)	938(81.78)
N1	586(22.31)	209(18.22)
Stage		
1A/B	1469(55.79)	696(60.68)
2A/B	1164(44.21)	451(39.32)
LVI		
Absent	1129(79.79)	890(80.25)
Present	286(20.21)	219(19.75)
PNI		
Absent	1232(88.32)	940(85.14)
Present	163(11.68)	164(14.86)
Surgery		
No	0(0.00)	0(0.00)
Yes	2633(100.00)	1147(100.00)
Chemotherapy		
No	1762(66.92)	775(67.57)
Yes	871(33.08)	372(32.43)
Recurrence Status		
Absent	2513(95.44)	1092(95.20)
Present	120(4.56)	55(4.80)
Survival Status		
Survived	2552(96.92)	1133(98.78)
Died	81(3.08)	14(1.22)
PR		
< 10	569(21.61)	282(24.59)
≥ 10	2064(78.39)	865(75.41)
Ki-67		
< 20	1841(69.92)	804(70.10)
≥ 20	792(30.08)	343(29.90)
PR10Ki20		
LR	1485(56.40)	625(54.49)
MR1	356(13.52)	179(15.61)
MR2	580(22.03)	240(20.92)
HiR	212(8.05)	103(8.98)

Notes: LR, PR ≥ 10% and Ki-67 < 20%; MR1, PR < 10% and Ki-67 < 20%; MR2, PR ≥ 10% and Ki-67 ≥ 20%; HiR, PR < 10% and Ki-67 ≥ 20%.

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion.

https://doi.org/10.2147/BCTT.S597707

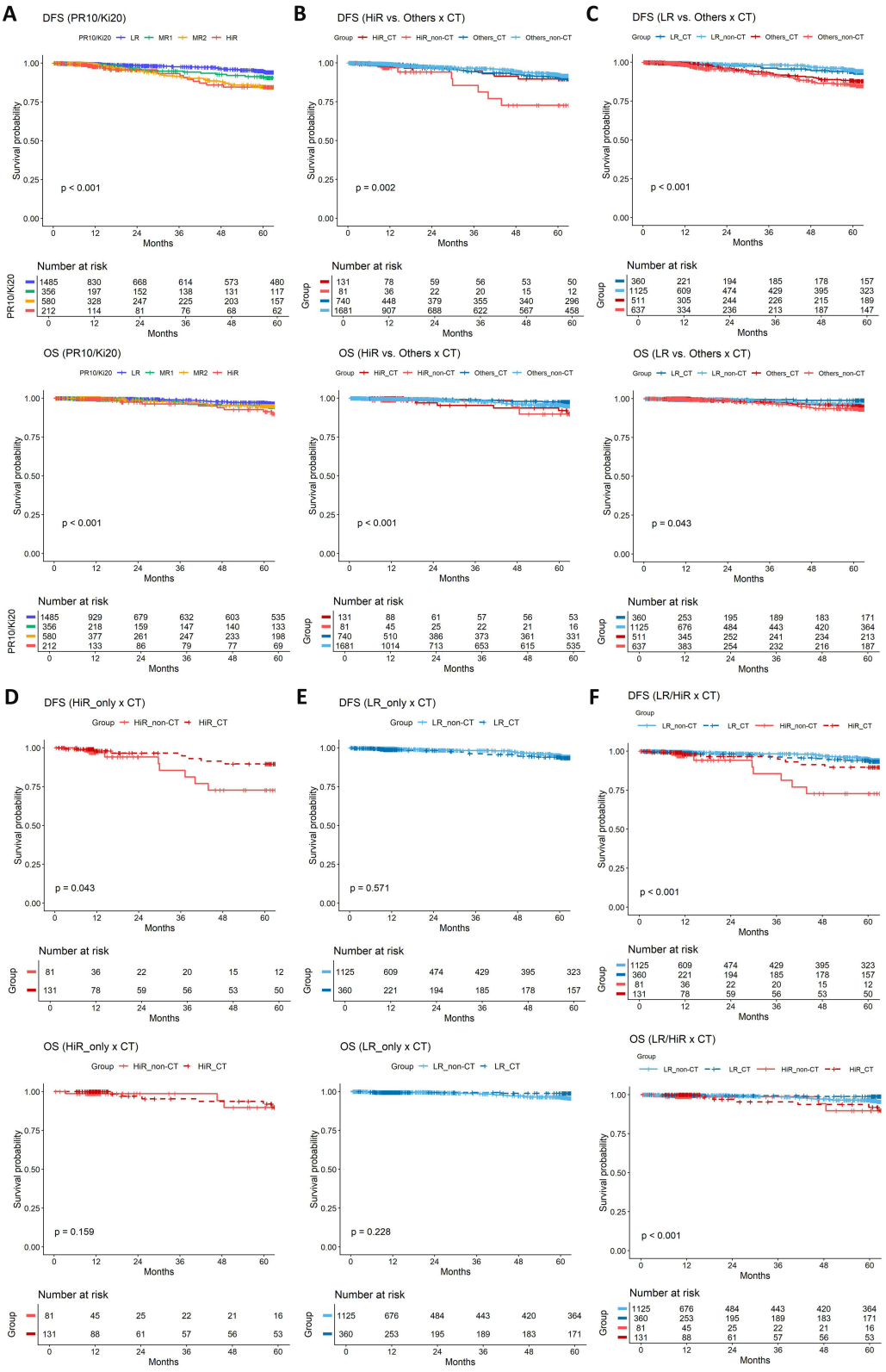

Figure 2 Kaplan-Meier survival analysis in the KMTTH discovery cohort. Upper panels represent DFS, and lower panels represent OS. (**A**) Prognostic stratification by PR10/Ki20 risk groups (LR, MR1, MR2, and HiR). (**B** and **C**) Survival comparisons stratified by CT status for (**B**) the HiR group vs. Others and (**C**) the LR group vs. Others. (**D** and **E**) Survival outcomes according to adjuvant CT receipt within the (**D**) HiR subgroup and (**E**) LR subgroup. (**F**) Direct comparison of survival outcomes between LR and HiR patients stratified by CT use. P-values were calculated using the Log rank test.

https://doi.org/10.2147/BCTT.S597707

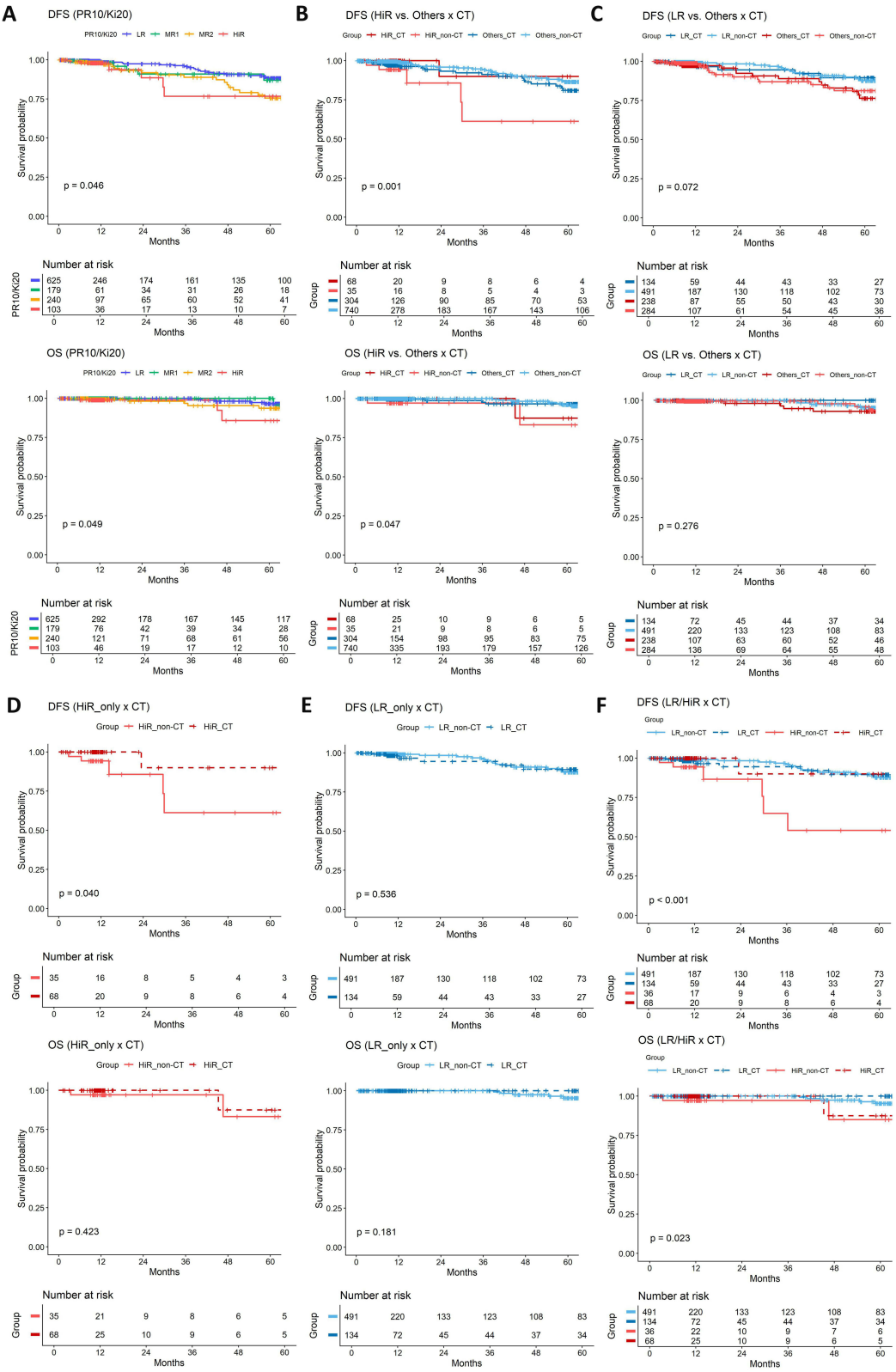

Figure 3 Kaplan-Meier survival analysis in the KMUH validation cohort. Upper panels represent DFS, and lower panels represent OS. (**A**) Prognostic stratification by PR10/Ki20 risk groups (LR, MR1, MR2, and HiR). (**B** and **C**) Survival comparisons stratified by CT status for (**B**) the HiR group vs. Others and (**C**) the LR group vs. Others. (**D** and **E**) Survival outcomes according to adjuvant CT receipt within the (**D**) HiR subgroup and (**E**) LR subgroup. (**F**) Direct comparison of survival outcomes between LR and HiR patients stratified by CT use. P-values were calculated using the Log rank test.

https://doi.org/10.2147/BCTT.S597707

Prognostic Stratification and Association with Chemotherapy Benefit

The model also identified subgroups with differential association between adjuvant CT and outcomes. In the KMTTH cohort, HiR patients receiving CT had improved DFS compared with HiR patients who did not (P = 0.043; Figure 2D). In contrast, CT was not associated with improved outcomes in the LR group (DFS, P = 0.571; OS, P = 0.228; Figure 2E). This pattern was reproduced in the KMUH cohort, where CT was associated with improved DFS in the HiR group (P = 0.040; Figure 3D) but not in the LR group (DFS, P = 0.536; OS, P = 0.181; Figure 3E). When analyses were simplified by comparing LR versus HiR, adjuvant CT remained strongly discriminatory in both cohorts (KMTTH: DFS and OS both P < 0.001; Figure 2F; KMUH: DFS, P < 0.001; OS, P = 0.023; Figure 3F). Collectively, these results suggest that PR10/Ki20 stratification can identify high-risk patients in whom CT is associated with improved DFS, while delineating low-risk patients without demonstrable CT benefit.

Multivariable Analysis and Incremental Prognostic Value

To assess whether PR10/Ki20 groups provided prognostic information beyond standard clinicopathological factors, multivariable Cox regression analyses were performed. In the KMTTH cohort, PR10/Ki20-defined HiR was an independent predictor of DFS (aHR 7.67; 95% CI 2.119–27.758; P = 0.0019; Table 2) after adjustment for age, pT stage, and LVI. In the KMUH cohort, both MR2 and HiR were associated with higher recurrence risk (Table 3). LVI remained a strong independent adverse factor in both cohorts. These findings support that PR10/Ki20 stratification provides incremental prognostic value beyond traditional clinicopathological parameters.

Association of Adjuvant Chemotherapy with DFS Within Risk Groups

A stratified analysis was conducted to evaluate the association between adjuvant CT and DFS within PR10/Ki20 risk groups. In the KMUH cohort, multivariable Cox regression demonstrated that CT was significantly associated with a reduced recurrence risk in the HiR group (aHR 0.075; 95% CI 0.006–0.919; P = 0.0428; Figure 4) after adjustment for age, pT stage, and LVI. Conversely, CT was not associated with improved outcomes in the LR group in either cohort. These results suggest that the association between adjuvant CT and improved DFS is predominantly confined to patients classified as HiR by the PR10/Ki20 model.

Development and Validation of a Quantitative Risk Score

To quantify cumulative prognostic burden, a quantitative *RS* was derived from the multivariable Cox model in the KMTTH cohort using regression coefficients (β = ln[aHR]). The *RS* was calculated as:

$$RS = 0.817\times MR1 + 0.514\times MR2 + 2.037\times HiR + 0.954\times(Age>45) + 0.093\times(pT2) + 1.483\times(LVI+).$$

Table 2 Univariate and Multivariable Cox Regression Analyses of Prognostic Factors for DFS in the KMTTH Cohort (n=2633)

Parameters	Comparison	Univariate Analysis		Multivariable Analysis		
		HR (95% CI)	p-value	aHR (95% CI)	p-value	β-value
PR10Ki20	MR1	3.26(0.728–14.592)	0.1223	2.263(0.481–10.666)	0.3020	0.817
	MR2	2.144(0.477–9.634)	0.3199	1.672(0.361–7.742)	0.5112	0.514
	HiR	9.136(2.645–31.556)	**0.0005**	7.67(2.119–27.758)	**0.0019**	2.037
Age	Age>45	2.342(0.535–10.254)	0.2588	2.595(0.579–11.633)	0.2130	0.954
Grade	Grade2	1.187(0.334–4.214)	0.7912			
	Grade3	1.226(0.202–7.448)	0.8252			
T	T2	2.368(0.905–6.193)	0.0789	1.097(0.371–3.248)	0.8671	0.093
N	N1	2.545(0.924–7.008)	0.0707			
Stage	Stage2	2.246(0.838–6.015)	0.1075			
LVI	LVI+	5.289(2.001–13.982)	**0.0008**	4.407(1.499–12.961)	**0.0070**	1.483
PNI	PNI+	0.563(0.074–4.284)	0.5787			

Note: Bold values indicate statistical significance (P < 0.05).

Table 3 Univariate and Multivariable Cox Regression Analyses of Prognostic Factors for DFS in the KMUH Cohort (n=1147)

Parameters	Comparison	Univariate Analysis		Multivariable Analysis	
		HR (95% CI)	p-value	aHR (95% CI)	p-value
PR10Ki20	MR1	1.352(0.543–3.371)	0.5170	1.311(0.514–3.346)	0.5705
	MR2	2.384(1.248–4.552)	**0.0085**	1.947(1.001–3.785)	**0.0496**
	HiR	2.957(1.182–7.396)	**0.0205**	2.743(1.087–6.924)	**0.0327**
Age	Age>45	0.709(0.375–1.338)	0.2879	0.716(0.374–1.373)	0.3151
Grade	Grade2	3.597(1.098–11.784)	**0.0345**		
	Grade3	6.184(1.788–21.394)	**0.0040**		
T	T2	1.347(0.762–2.383)	0.3052	1.060(0.588–1.911)	0.8468
N	N1	1.993(1.086–3.660)	**0.0261**		
Stage	Stage2	1.320(0.753–2.314)	0.3319		
LVI	LVI+	3.102(1.754–5.484)	**<0.0001**	2.674(1.476–4.847)	**0.0012**
PNI	PNI+	1.096(0.532–2.260)	0.8038		

Note: Bold values indicate statistical significance (P < 0.05).

Patients were categorized into low-*RS* and high-*RS* groups using the cohort-specific median *RS* as the cutoff. In the KMTTH cohort, the high-*RS* group had significantly worse DFS (P = 0.005) and OS (P = 0.001) compared with the low-*RS* group (Figure 5A). In the KMUH cohort, high *RS* was similarly associated with inferior DFS (P = 0.004; Figure 5B). Although OS differences showed a consistent direction, they did not reach statistical significance (P = 0.165). Together, these results support the *RS* as a reproducible quantitative tool for identifying patients at elevated recurrence risk across independent cohorts.

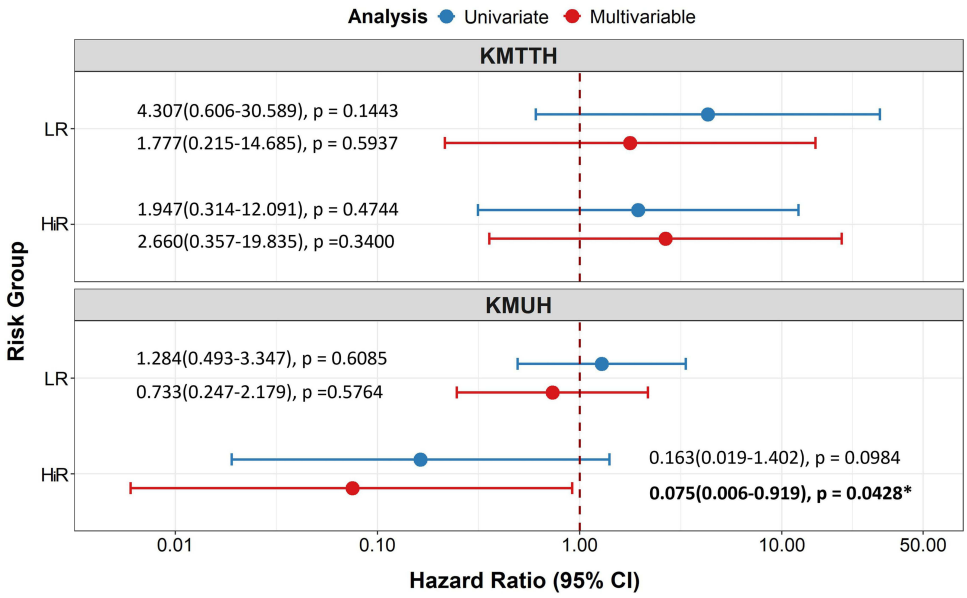

Figure 4 Forest plot analysis of the association between adjuvant chemotherapy receipt and DFS stratified by PR10/Ki20 risk groups. The forest plots display hazard ratios (HRs) for DFS comparing patients who received adjuvant CT versus those who did not, in the KMTTH and KMUH cohorts, stratified into LR and HiR subgroups. Blue dots represent unadjusted HRs from univariate analysis, while red dots represent adjusted HRs (aHRs) from multivariable analysis. Horizontal lines indicate 95% confidence intervals (95% CIs). The vertical dashed line represents the null value (HR = 1.0); values < 1.0 indicate lower hazard in the adjuvant chemotherapy group. Multivariable models were adjusted for age, pathological T stage (pT), and lymphovascular invasion (LVI). Text labels indicate HR/aHR (95% CI) and p-values, with bold text indicating statistical significance (p < 0.05).
Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio.

https://doi.org/10.2147/BCTT.S597707

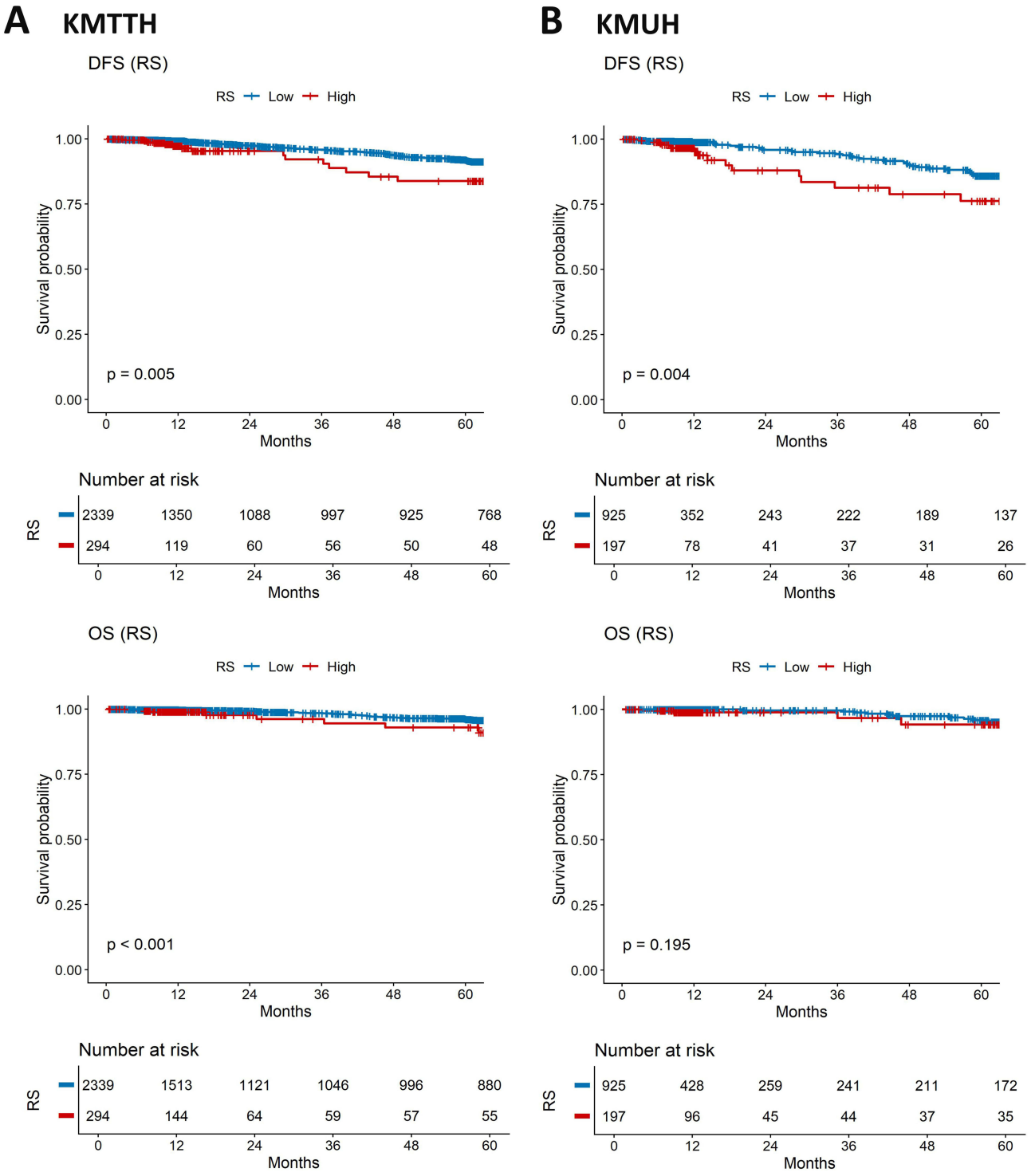

Figure 5 Prognostic performance of the quantitative Risk Score (RS) in the discovery and validation cohorts. Kaplan-Meier survival estimates for DFS (upper panels) and OS (lower panels) in the (**A**) KMTTH (discovery) and (**B**) KMUH (validation) cohorts. The *RS* was derived from a multivariable Cox regression model incorporating PR10/Ki20 categories, age, pathological T stage (pT), and LVI. Patients were stratified into low-*RS* and high-*RS* groups using the cohort-specific median *RS* as the cutoff. P-values were calculated using the Log rank test.

Discussion

In this large dual-cohort retrospective study, we demonstrated that an IHC-based stratification using the PR10/Ki20 framework provides consistent prognostic information for patients with HR+/HER2− early breast cancer and identifies

 https://doi.org/10.2147/BCTT.S597707

subgroups with differential outcomes according to adjuvant CT receipt. Using prespecified cutoffs (PR < 10% and Ki-67 ≥ 20%), we identified a high-risk subgroup with inferior DFS and OS across two independent cohorts. Importantly, adjuvant CT was associated with improved DFS in the HiR group, whereas no statistically significant association was observed in the substantial LR population. Together, these findings may help inform risk-adapted discussions and generate hypotheses for prospective validation, with the goal of reducing overtreatment in routine practice.

Ki-67 and PR have long been central to luminal breast cancer classification; however, clinical implementation has been limited by interobserver variability and uncertainty regarding optimal thresholds.[25] The adoption of higher Ki-67 cutoffs (eg, 20%) following the 2013 St. Gallen consensus aimed to improve reproducibility and reduce overclassification of luminal B disease.[15] Likewise, while PR positivity (≥1%) indicates endocrine responsiveness, accumulating evidence suggests that low PR expression reflects impaired estrogen signaling and more aggressive tumor biology.[17,26] In this context, a PR < 10% cutoff may provide greater specificity than higher thresholds when interpreted jointly with Ki-67. Importantly, our results suggest that neither biomarker alone is sufficient for optimal risk stratification; rather, the combination of PR < 10% and Ki-67 ≥ 20% delineates a subgroup with unfavorable outcomes, consistent with the biological convergence of endocrine resistance and high proliferative activity. This dual-marker approach may reduce misclassification inherent to single-parameter models and offers an intuitive pathology-based risk stratification tool. Although Ki-67 has also been associated with prognosis in HER2+ and triple-negative breast cancer (TNBC), the PR10/Ki20 framework was developed and validated for HR+/HER2− disease and relies on PR expression, which is typically absent in TNBC. Therefore, it should not be extrapolated to non-luminal subtypes without dedicated subtype-specific validation.

Across both the discovery (KMTTH) and validation (KMUH) cohorts, adjuvant CT was associated with improved DFS primarily in the HiR group, whereas no statistically significant association was observed in the LR group. In the validation cohort, multivariable analysis confirmed that adjuvant CT was associated with significantly improved DFS in the HiR group (aHR 0.075; 95% CI 0.006–0.919; P = 0.0428; Figure 4). However, the wide confidence interval suggests limited event numbers and reduced estimate stability; thus, the estimated magnitude of this association should be interpreted cautiously and confirmed in larger cohorts. These findings indicate that a refined IHC-based algorithm may serve as a practical triage tool in settings where multigene assays (eg, Oncotype DX, MammaPrint) are unavailable or cost-prohibitive, although prospective studies are needed to benchmark its performance and clarify its role relative to genomic testing. To further quantify individualized risk, we developed a quantitative *RS* integrating PR10/Ki20 categories with established clinicopathological variables. The *RS* consistently separated patients into high- and low-risk groups with significantly different DFS in both cohorts (KMTTH, P = 0.005; KMUH, P = 0.004; Figure 5), supporting generalizability. LVI remained a strong independent prognostic factor, highlighting the continued importance of classical pathological features. While IHC biomarkers reflect intrinsic tumor biology, LVI captures the phenotype of tumor–stroma interaction and systemic dissemination potential; thus, incorporating both dimensions may improve risk estimation. In contexts where genomic testing is delayed or unavailable, the *RS* provides a pragmatic approach to risk quantification.

Clinically, most patients in both cohorts were classified as LR by PR10/Ki20 and experienced excellent outcomes. In this retrospective analysis, we did not observe a statistically significant association between adjuvant CT receipt and DFS in this majority population. While this finding raises the hypothesis that some low-risk patients may be able to avoid CT, such an approach should be evaluated in prospective studies before being adopted in practice, particularly given the potential for confounding in retrospective treatment allocation. Conversely, the model identifies a smaller but clinically important HiR subgroup (~8–9%) with poorer prognosis and evidence of CT-associated DFS improvement, suggesting that these patients merit further study in prospective, risk-adapted treatment strategies. Several limitations should be acknowledged. First, the retrospective design is subject to selection bias and unmeasured confounding in treatment allocation. Although our large cohorts improve precision, residual confounding cannot be fully excluded. Second, variability in Ki-67 scoring across laboratories and limited event numbers in some subgroups may affect estimate stability. Third, we did not directly compare PR10/Ki20 with multigene assays. Prospective multicenter validation, benchmarking against additional prognostic markers/risk models, and sensitivity analyses are warranted to confirm robustness and define its role in clinical workflows. Finally, subtype-specific validation is required before applying this framework to HER2-positive or triple-negative breast cancers. In practice, PR10/Ki20 may help triage patients when chemotherapy decisions are uncertain and prioritize multigene testing for intermediate cases, pending prospective validation.

Conclusion

In summary, the PR10/Ki20 framework provides an accessible and biologically grounded approach for prognostic stratification and for identifying patient subgroups with differential outcomes associated with adjuvant CT in HR +/HER2− early breast cancer. Integrating these IHC markers with clinicopathological factors may help inform risk-adapted treatment discussions; however, further prospective validation is needed to determine whether and how this framework could be incorporated into treatment selection and to evaluate escalation or de-escalation strategies.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Chi-Wen Luo, upon reasonable request.

Acknowledgments

This study was supported by the following grants: (1) Grants 114-2320-B-037-002 from the National Science and Technology Council, Taiwan; (2) Grant KMUGH-114-019 from Kaohsiung Medical University Gangshan Hospital, Kaohsiung, Taiwan.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Prat A, Pineda E, Adamo B, et al. Clinical implications of the intrinsic molecular subtypes of breast cancer. *Breast*. 2015;24(Suppl 2):S26–S35. doi:10.1016/j.breast.2015.07.008
2. Nolan E, Lindeman GJ, Visvader JE. Deciphering breast cancer: from biology to the clinic. *Cell*. 2023;186(8):1708–1728. doi:10.1016/j.cell.2023.01.040
3. Atallah NM, Haque M, Quinn C, et al. Characterisation of luminal and triple-negative breast cancer with HER2 low protein expression. *Eur J Cancer*. 2023;195:113371. doi:10.1016/j.ejca.2023.113371
4. Orrantia-Borunda E, Anchondo-Nunez P, Acuna-Aguilar LE, Gomez-Valles FO, Ramirez-Valdespino CA. Subtypes of breast cancer. In: Mayrovitz HN, editor. *Breast Cancer*. Exon Publications; 2022.
5. Inic Z, Zegarac M, Inic M, et al. Difference between luminal A and luminal B subtypes according to Ki-67, tumor size, and progesterone receptor negativity providing prognostic information. *Clin Med Insights Oncol*. 2014;8:107–111. doi:10.4137/CMO.S18006
6. Ahn HJ, Jung SJ, Kim TH, Oh MK, Yoon HK. Differences in clinical outcomes between luminal a and b type breast cancers according to the St. Gallen Consensus 2013. *J Breast Cancer*. 2015;18(2):149–159. doi:10.4048/jbc.2015.18.2.149
7. Gouveia MC, Scaranti M, Migliavacca Zucchetti B, Bonadio RC, Barroso-Sousa R, Leone JP. Unveiling the paradigm shift: systemic treatment strategies in small, node-negative breast cancer. *NPJ Breast Cancer*. 2025;11(1):44. doi:10.1038/s41523-025-00761-8
8. Park YH, Kim ST, Cho EY, et al. A risk stratification by hormonal receptors (ER, PgR) and HER-2 status in small (< or = 1 cm) invasive breast cancer: who might be possible candidates for adjuvant treatment? *Breast Cancer Res Treat*. 2010;119(3):653–661. doi:10.1007/s10549-009-0665-x
9. Vasconcellos JM, Bonadio RC, Mendes SV, et al. Does undertreatment with chemotherapy impact the outcomes of elderly patients with early-stage breast cancer? A real-world data analysis. *Clin Breast Cancer*. 2025;25(5):472–480e3. doi:10.1016/j.clbc.2025.02.007
10. Bhattacharyya GS, Doval DC, Desai CJ, Chaturvedi H, Sharma S, Somashekhar SP. Overview of breast cancer and implications of overtreatment of early-stage breast cancer: an indian perspective. *JCO Glob Oncol*. 2020;6(6):789–798. doi:10.1200/GO.20.00033
11. Brogna MR, Ferrara G, Varone V, et al. Evaluation and comparison of prognostic multigene tests in early-stage breast cancer: which is the most effective? A literature review exploring clinical utility to enhance therapeutic management in luminal patients. *Mol, Carcinog*. 2025;64(5):789–800. doi:10.1002/mc.23893
12. Hsieh TY, Huang CC, Tseng LM. Multi-gene expression assays in breast cancer: a literature review. *Transl Cancer Res*. 2025;14(9):6092–6101. doi:10.21037/tcr-2025-803
13. Finkelman BS, Zhang H, Hicks DG, Turner BM. The evolution of Ki-67 and breast carcinoma: past observations, present directions, and future considerations. *Cancers*. 2023;15(3):808. doi:10.3390/cancers15030808
14. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer 2011. *Ann Oncol*. 2011;22(8):1736–1747. doi:10.1093/annonc/mdr304

15. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2013. *Ann Oncol*. 2013;24(9):2206–2223. doi:10.1093/annonc/mdt303
16. Lombardi A, Lazzeroni R, Bersigotti L, Vitale V, Amanti C. The proper Ki-67 cut-off in hormone responsive breast cancer: a monoinstitutional analysis with long-term follow-up. *Breast Cancer*. 2021;13:213–217. doi:10.2147/BCTT.S305440
17. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med*. 2010;134(7):e48–e72. doi:10.5858/134.7.e48
18. Prat A, Cheang MC, Martin M, et al. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. *J Clin Oncol*. 2013;31(2):203–209. doi:10.1200/JCO.2012.43.4134
19. Yersal O, Barutca S. Biological subtypes of breast cancer: prognostic and therapeutic implications. *World J Clin Oncol*. 2014;5(3):412–424. doi:10.5306/wjco.v5.i3.412
20. Cui X, Schiff R, Arpino G, Osborne CK, Lee AV. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. *J Clin Oncol*. 2005;23(30):7721–7735. doi:10.1200/jco.2005.09.004
21. Cheang MC, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst*. 2009;101(10):736–750. doi:10.1093/jnci/djp082
22. Nishimukai A, Yagi T, Yanai A, et al. High Ki-67 expression and low progesterone receptor expression could independently lead to a worse prognosis for postmenopausal patients with estrogen receptor-positive and HER2-negative breast cancer. *Clin Breast Cancer*. 2015;15(3):204–211. doi:10.1016/j.clbc.2014.12.007
23. Kwak Y, Jang SY, Choi JY, et al. Progesterone receptor expression level predicts prognosis of estrogen receptor-positive/HER2-negative young breast cancer: a single-center prospective cohort study. *Cancers*. 2023;15(13). doi:10.3390/cancers15133435
24. Bardou VJ, Arpino G, Elledge RM, Osborne CK, Clark GM. Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. *J Clin Oncol*. 2003;21(10):1973–1979. doi:10.1200/jco.2003.09.099
25. Davey MG, Hynes SO, Kerin MJ, Miller N, Lowery AJ. Ki-67 as a prognostic biomarker in invasive breast cancer. *Cancers*. 2021;13(17). doi:10.3390/cancers13174455
26. Yu KD, Cai YW, Wu SY, Shui RH, Shao ZM. Estrogen receptor-low breast cancer: biology chaos and treatment paradox. *Cancer Commun*. 2021;41(10):968–980. doi:10.1002/cac2.12191