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Association Between the Preoperative Systemic Immune- Inflammation Index and Pathologic Complete Response AfterNeoadjuvant Therapy for Breast Cancer A Retrospective Cohort Study With Internal Validation

Tianle Cheng

ctldeGreenTea@outlook.com

Jiamusi University

Research Article

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Abstract

Background

Pathologic complete response (pCR) after neoadjuvant systemic therapy is an important treatment endpoint in breast cancer. Peripheral blood inflammatory indices may provide low-cost pretreatment predictive information, but their incremental value beyond clinicopathologic characteristics remains uncertain.

Methods

We retrospectively analyzed 429 registry records corresponding to 427 medical record identifiers. The primary outcome was defined using a strict operational definition of pCR restricted to records coded as exactly 0 or 1 in the original field. The systemic immune-inflammation index (SII) was calculated as platelet count x neutrophil count/lymphocyte count. Multivariable logistic regression was used to evaluate the association between SII and pCR after adjustment for age, clinical T stage, clinical N stage, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 immunohistochemistry (IHC). A clinical model was compared with a model that additionally included SII. We report the area under the receiver operating characteristic curve (AUC), Brier score, calibration, and internal validation based on 500 bootstrap resamples.

Results

Strictly defined pCR status was available for 389 patients, of whom 80 achieved pCR (20.6%). The complete-case dataset for the primary model included 343 patients and 74 pCR events. Median SII was lower in the pCR group than in the non-pCR group (448.35 vs 544.23; P = 0.010). Higher log-transformed SII was independently associated with a lower probability of pCR (odds ratio [OR], 0.56; 95% confidence interval [CI], 0.37–0.85; P = 0.006). In the same 343-patient complete-case dataset, adding SII increased the apparent AUC from 0.716 to 0.731. Optimism-corrected AUCs were 0.686 for the clinical model and 0.700 for the clinical-plus-SII model. Across ascending SII quartiles, pCR rates were 24.7%, 26.8%, 19.6%, and 10.8%, respectively. In a sensitivity analysis using the expanded pCR definition, the corresponding OR was 0.70 (95% CI, 0.48–1.03; P = 0.074).

Conclusions

Preoperative SII was independently associated with pCR and provided a small but consistent improvement in internal predictive performance beyond a clinicopathologic model. SII may serve as a low-cost adjunct to routinely available clinicopathologic information, although its transportability requires validation in independent cohorts.

Introduction

Breast cancer is one of the most common malignancies among women worldwide and is characterized by substantial biological heterogeneity and variation in treatment response. Neoadjuvant systemic therapy can reduce tumor burden, increase the likelihood of breast-conserving surgery, and permit in vivo assessment of tumor sensitivity to systemic treatment. Achieving pCR after treatment is generally associated with favorable long-term outcomes, although the strength of this association varies according to molecular subtype and treatment strategy.1,2

Neutrophils, lymphocytes, monocytes, and platelets reflect aspects of host inflammation, immune status, and the tumor microenvironment. Composite indices derived from these cell counts, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and SII, have been investigated as prognostic markers and predictors of response to neoadjuvant therapy in breast cancer. Recent studies have evaluated pretreatment PLR and NLR, PLR-based nomograms, inflammatory markers in HER2-positive cohorts, SII-based pCR models, and dynamic changes in SII and the prognostic nutritional index. However, study populations, molecular subtypes, treatment regimens, blood sampling windows, pCR definitions, cutoff values, and validation strategies have varied considerably, precluding direct comparison of effect estimates across studies.3–8

A clinically useful biomarker should not only be statistically associated with the outcome but should also provide quantifiable predictive information beyond routinely available clinicopathologic factors. We therefore evaluated SII as a continuous variable in relation to pCR, compared several inflammatory indices, performed sensitivity analyses using strict and expanded pCR definitions, and assessed internal predictive performance by bootstrap resampling in a common complete-case dataset.

Materials and Methods

Study Design and Participants

This retrospective observational cohort study was based on a deidentified registry workbook and was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, with reference to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) principles. The workbook contained 429 records corresponding to 427 medical record identifiers; four records were associated with duplicated identifiers. Eligible participants were patients with breast cancer who received preoperative systemic therapy and subsequently underwent surgery. Records were excluded as appropriate because of duplicated identifiers, missing pCR status, or missing pretreatment complete blood count data.

Outcome Definition and Candidate Indices

The primary outcome was pCR. Because the original pCR field contained both numeric and text entries, the primary analysis included only records in which the original value was exactly 0 (non-pCR) or 1 (pCR). In the sensitivity analysis, nonmissing text entries beginning with 0 or 1 were classified according to the first digit. Pretreatment blood cell counts were used to calculate NLR, PLR, SII, and LMR. SII, NLR, PLR, LMR, fibrinogen, and D-dimer were natural log-transformed before inclusion in regression models. Clinical adjustment variables included age, T stage, N stage, ER status, PR status, and HER2 IHC score; T and N stage were modeled as ordinal variables according to their original coding.

Statistical Analysis

Continuous variables are summarized as medians and interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Between-group comparisons were performed using the Wilcoxon rank-sum test, chi-square test, or Fisher exact test, as appropriate. A multivariable logistic regression model was fitted with pCR as the dependent variable and log(SII) as the primary independent variable, adjusting for age, T stage, N stage, ER status, PR status, and HER2 IHC score. A clinical model containing only clinicopathologic variables was compared with an extended model that additionally included SII. Both models were fitted in the same complete-case dataset of 343 patients. Apparent AUC, Brier score, and calibration were evaluated. A total of 500 bootstrap resamples were used to estimate optimism in the AUC and characterize the distribution of the incremental AUC. Potential nonlinearity was assessed in a sensitivity analysis using a natural spline for log(SII).

Results

Study Population and Analysis Sets

Of the 429 registry records, 389 had strictly defined pCR information; 80 patients achieved pCR, corresponding to a pCR rate of 20.6%. Complete pretreatment blood count data were available for 412 patients. The complete-case dataset for the primary model comprised 343 patients, including 74 pCR events. The derivation of the study population, outcome availability, and primary model dataset is shown in Fig. 1.

Baseline Characteristics

Selected baseline characteristics according to strictly defined pCR status are presented in Table 1. Compared with the non-pCR group, the pCR group generally had a smaller recorded maximum tumor diameter, lower platelet count, NLR, PLR, and SII, and a higher Ki-67 index. The proportions of ER-negative, PR-negative, and HER2 IHC 3 + tumors were also higher in the pCR group. Because the outcome and covariates contained missing values, denominators varied across variables.

Table 1
Selected baseline characteristics according to strictly defined pCR status

Variable	Non-pCR group	pCR group	P value
No. of patients	309	80	-
Age, years	48.00 (40.00–56.00)	48.50 (41.00–56.00)	0.799
Recorded maximum tumor diameter	36.00 (26.00–47.00)	30.00 (21.50–44.00)	0.011
Platelet count	254.00 (211.00-293.00)	235.00 (188.50-281.50)	0.030
Ki-67, %	20.00 (8.00–35.00)	30.00 (20.00–40.00)	0.002
NLR	2.19 (1.59–3.04)	1.98 (1.46–2.62)	0.042
PLR	130.41 (104.20-177.51)	121.92 (95.72-147.66)	0.018
SII	544.23 (367.29-856.55)	448.35 (321.68-646.56)	0.010
ER-positive	202 (65.4%)	27 (33.8%)	< 0.001
PR-positive	163 (52.8%)	17 (21.2%)	< 0.001
HER2 IHC 3+	77 (28.2%)	37 (49.3%)	< 0.001

Unless otherwise indicated, values are median (IQR) or n/N (%). SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Association Between SII and pCR

Median SII was lower in the pCR group than in the non-pCR group (448.35 vs 544.23; Wilcoxon P = 0.010). Across ascending SII quartiles, pCR rates were 24.7%, 26.8%, 19.6%, and 10.8%, respectively.

In multivariable logistic regression, higher log(SII) was independently associated with lower odds of pCR (OR, 0.56; 95% CI, 0.37–0.85; P = 0.006). This OR represents a 1-unit increase in the natural logarithm of SII. PR status and T stage were also independently associated with pCR. The natural spline model did not provide a significantly better fit than the linear log(SII) model (likelihood ratio test P = 0.237).

Table 2
Multivariable logistic regression analysis of strictly defined pCR

Variable	OR	95% CI	P value
log(SII)	0.56	0.37–0.85	0.006
Age, per 1-year increase	0.99	0.97–1.02	0.666
T stage, per 1-level increase	0.65	0.43–0.99	0.047
N stage, per 1-level increase	1.04	0.76–1.44	0.793
ER-positive	0.51	0.23–1.14	0.099
PR-positive	0.40	0.16–0.96	0.041
HER2 IHC, per 1-level increase	1.11	0.89–1.38	0.354

Complete-case dataset: n = 343, including 74 pCR events. SII was natural log-transformed. ER-positive and PR-positive status were coded relative to ER-negative and PR-negative status, respectively.

Comparison of Inflammatory Indices and Model Performance

In alternative models, PLR and NLR were associated with lower odds of pCR, whereas the association for LMR was weaker. Complete-case samples were smaller for fibrinogen and D-dimer; these estimates should therefore be interpreted cautiously. The apparent AUC was 0.716 for the clinical model and 0.731 after SII was added; the corresponding Brier scores were 0.153 and 0.149. Because complete-case datasets differed among candidate indices, their performance should not be compared directly without accounting for differences in the analyzed samples.

Table 3
Apparent predictive performance of candidate models

Model	Complete cases	pCR events	AUC	Brier score
Clinical model (SII complete cases)	343	74	0.716	0.153
Clinical model + SII	343	74	0.731	0.149
Clinical model + PLR	343	74	0.733	0.149
Clinical model + NLR	343	74	0.722	0.152
Clinical model + LMR	343	74	0.718	0.153
Clinical model + fibrinogen	333	71	0.742	0.147
Clinical model + D-dimer	197	42	0.725	0.149

The clinical model included age, T stage, N stage, ER status, PR status, and HER2 IHC score. Unless otherwise indicated, values represent apparent performance in the complete-case dataset for each model.

Sensitivity Analysis and Exploratory Survival Analysis

Using the expanded pCR definition, the adjusted OR for log(SII) was 0.70 (95% CI, 0.48–1.03; P = 0.074; n = 358). In the exploratory date-based survival analysis, 395 records had valid date intervals for both overall survival (OS) and disease-free survival (DFS). Among patients with complete data for strictly defined pCR and model covariates, the OS analysis included 346 patients and 110 deaths, whereas the DFS analysis included 346 patients and 152 recurrences. In adjusted Cox models, pCR was associated with a hazard ratio (HR) of 0.64 for OS (95% CI, 0.38–1.07; P = 0.090) and 0.60 for DFS (95% CI, 0.38–0.94; P = 0.027). Because survival outcomes were reconstructed from registry date fields, these findings should be considered descriptive and exploratory.

Table 4
Exploratory date-based survival analysis

Endpoint	Records with valid dates	Patients in model	Events in model	Adjusted HR for pCR	95% CI	P value
Overall survival (OS)	395	346	110	0.64	0.38–1.07	0.090
Disease-free survival (DFS)	395	346	152	0.60	0.38–0.94	0.027

OS and DFS were reconstructed from registry date fields. Cox models were adjusted for age, T stage, N stage, ER status, and HER2 IHC score. Log-rank P values comparing strictly defined pCR groups were 0.046 for OS and 0.006 for DFS.

Discussion

In this retrospective cohort study, lower preoperative SII was associated with a higher probability of pCR. The association persisted after adjustment for age, T and N stage, and receptor status. Across SII quartiles, pCR rates ranged from 24.7% to 10.8%. In the same complete-case dataset of 343 patients, adding SII increased the apparent AUC from 0.716 to 0.731, indicating a modest improvement in internal predictive performance.

Our findings are consistent with previous studies investigating peripheral blood inflammatory indices as predictors of response to neoadjuvant therapy in breast cancer, but they should not be presented as the first evidence of such an association. Prior studies have examined pretreatment PLR and NLR, PLR-based nomograms, inflammatory markers in HER2-positive populations, SII-based pCR models, and changes in SII and the prognostic nutritional index during treatment.3–8 Collectively, these studies support the rationale for evaluating routine blood-based measures as low-cost candidate biomarkers

while suggesting that effect estimates may depend on molecular subtype, treatment regimen, blood sampling time point, outcome definition, and modeling strategy.

We modeled SII as a continuous log-transformed variable rather than applying a data-driven binary cutoff. This approach was chosen to reduce information loss and avoid interpreting a cohort-specific threshold as universally applicable. Previous SII nomogram studies have often used receiver operating characteristic-derived cutoffs and incorporated variables such as Ki-67, treatment cycles, and carcinoembryonic antigen. More recent prediction studies have emphasized reporting calibration, Brier scores, and internal validation within a common analysis set, followed by independent external validation when feasible.7,9–12 We therefore reported statistical association separately from incremental predictive performance and did not interpret the small change in AUC as evidence of clinical benefit.

Biologically, neutrophils may contribute to a protumor inflammatory microenvironment, lymphocytes reflect antitumor immune responses, and platelets may participate in tumor cell survival, vascular interactions, and inflammatory signaling. By integrating these components, SII may capture host-tumor interactions more comprehensively than any single cell count. Nevertheless, observational data cannot distinguish the role of the inflammatory index itself from shared causes such as tumor burden, infection, medication use, or comorbidities. The observed association therefore should not be interpreted as causal.3

Strengths of this study include the concurrent comparison of multiple inflammatory and coagulation indices in a single dataset; use of a strict pCR field for the primary analysis; modeling of SII as a continuous variable; bootstrap correction for optimism; and comparison of the clinical and extended models within the same SII complete-case dataset. Several limitations should also be acknowledged. The retrospective design precludes causal inference. The source data included text entries for pCR, inconsistently coded stage and treatment regimens, duplicated medical record identifiers, and missing HER2 and coagulation data. The pretreatment blood sampling window and pathologic details were not fully standardized. Date-based OS and DFS outcomes were reconstructed for exploratory purposes. Finally, all performance estimates were derived internally, and the model has not undergone external validation.

In conclusion, preoperative SII was independently associated with pCR after neoadjuvant therapy for breast cancer and provided a modest improvement in internal predictive performance beyond clinicopathologic variables. SII may be better considered a low-cost adjunct to routine clinicopathologic information than a standalone basis for treatment decisions.

Declarations

Consent to publish

Not applicable. This manuscript does not contain any individual person's identifiable data (including images, videos, or detailed individual case information). All patient data were anonymized and are presented in aggregate form only.

Ethics approval and consent to participate

This retrospective study was approved by the Harbin Medical University Cancer Hospital. The study was conducted in accordance with the Declaration of Helsinki and its later amendments. No experiments were performed on human participants, and no participants were recruited for this study. All data were obtained from existing medical records generated during routine clinical care, and patient information was anonymized prior to analysis. Therefore, the requirement for informed consent to participate was waived by the Harbin Medical University Cancer Hospital due to the retrospective nature of the study.

Author Contribution

T.L. Cheng wrote the manuscript and prepared all figures and tables.

Data Availability

The data that support the findings of this study are available from Harbin Medical University Cancer Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Harbin Medical University Cancer Hospital.

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Figures

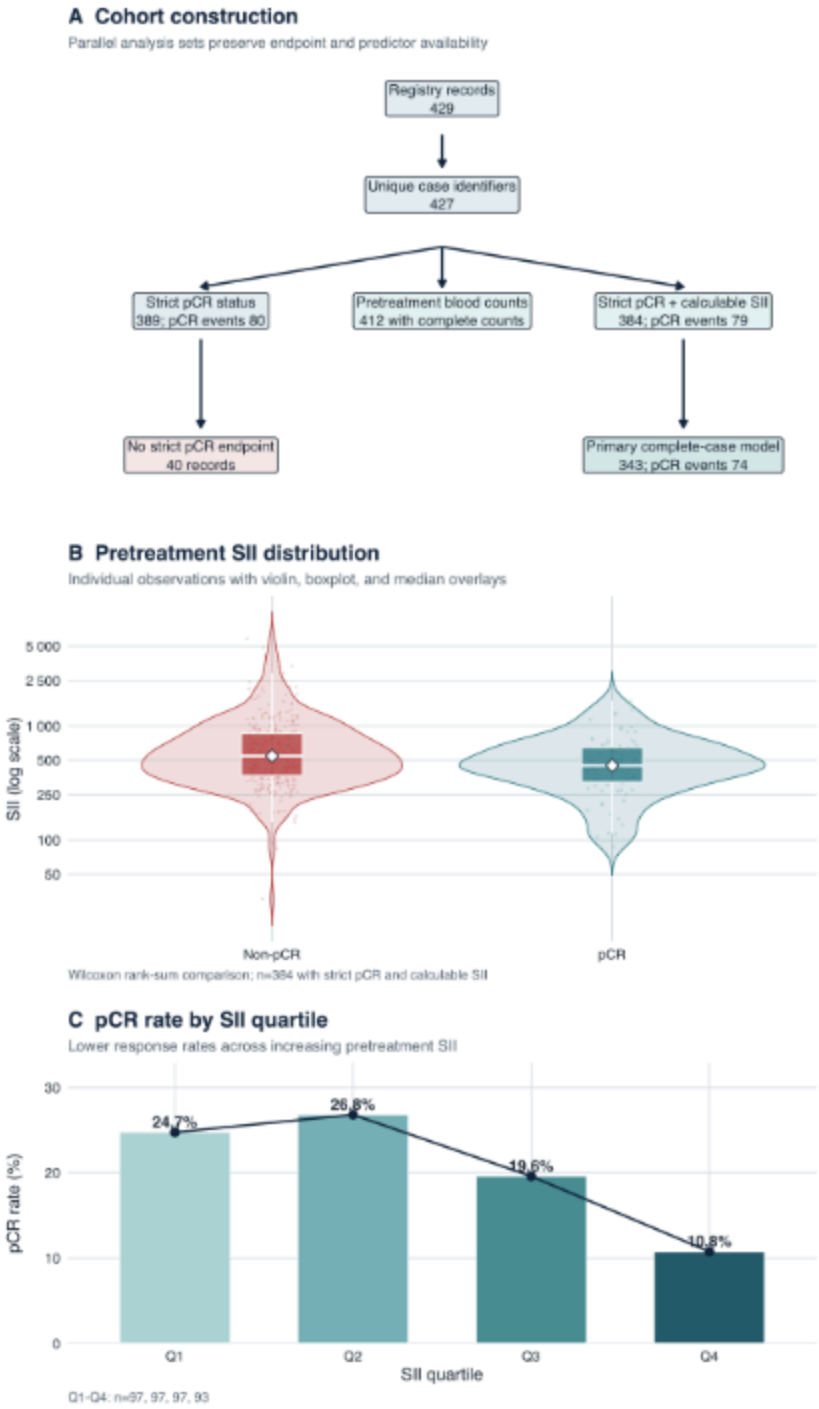


Figure 1

Study cohort, distribution of preoperative SII, and pCR rates by SII quartile. (A) Derivation of the analysis set from registry records to the complete-case dataset for the primary model. (B) Individual-level distribution of SII according to strictly defined pCR status. (C) pCR rates across quartiles of SII. SII, systemic immune-inflammation index; pCR, pathologic complete response.

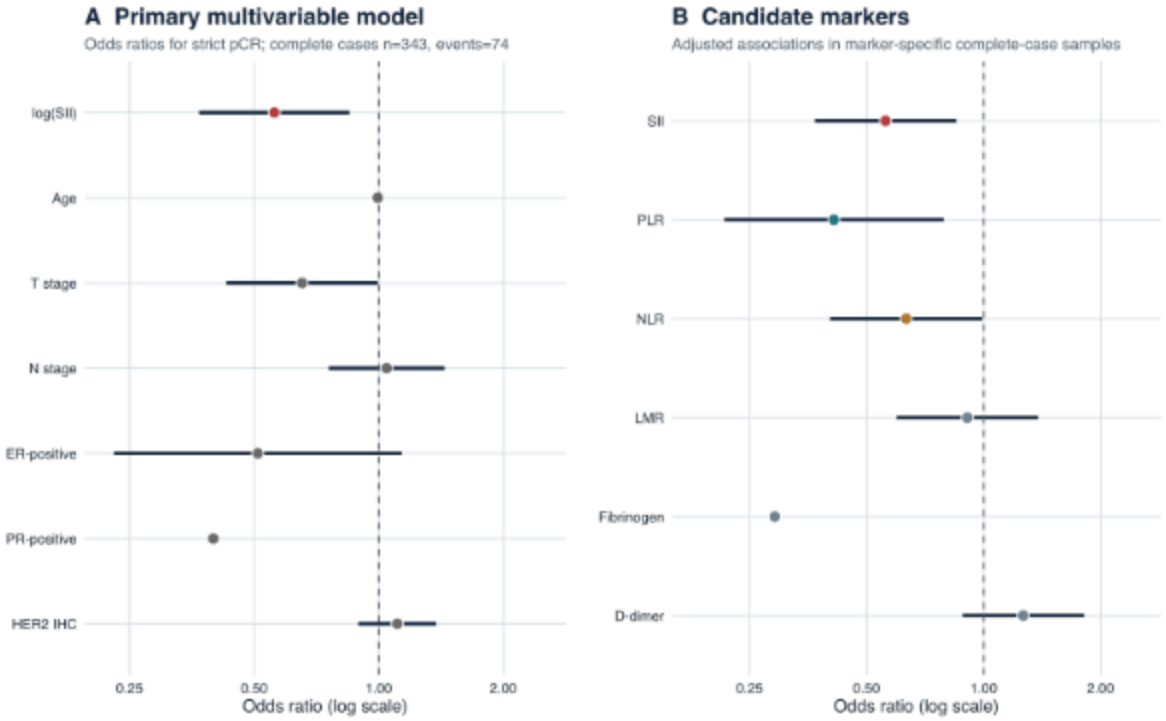


Figure 2

Multivariable logistic regression results. (A) Associations of variables in the primary model with strictly defined pCR. (B) Adjusted associations of SII, PLR, NLR, LMR, fibrinogen, and D-dimer with pCR in their respective complete-case datasets. Points indicate ORs and lines indicate 95% CIs; the dashed line denotes an OR of 1.

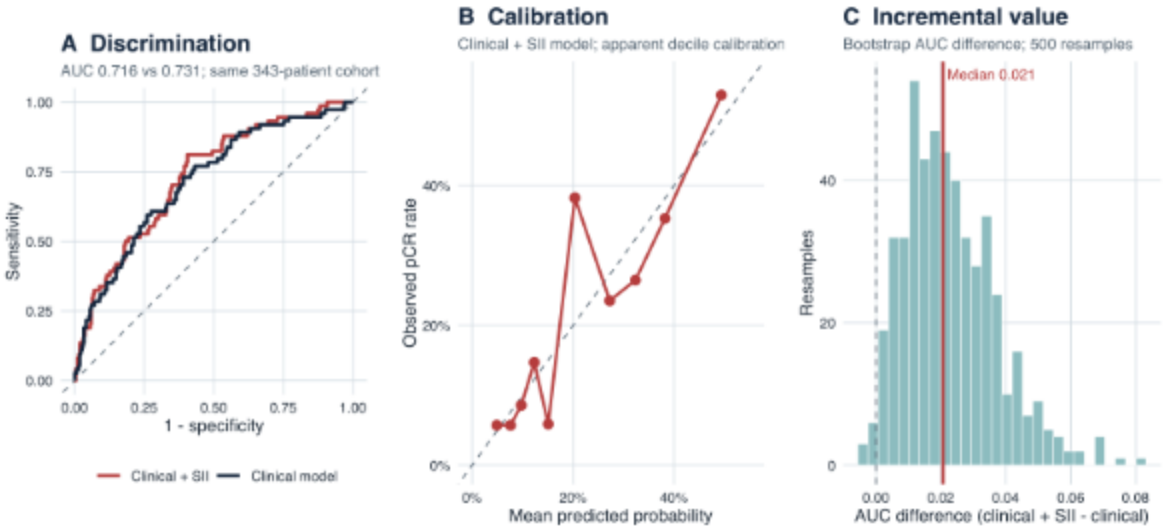


Figure 3

Predictive performance of the models. (A) Receiver operating characteristic curves for the clinical model and the clinical-plus-SII model. (B) Apparent calibration plot for the clinical-plus-SII model. (C) Distribution of the incremental AUC across 500 bootstrap resamples; the red line indicates the median.

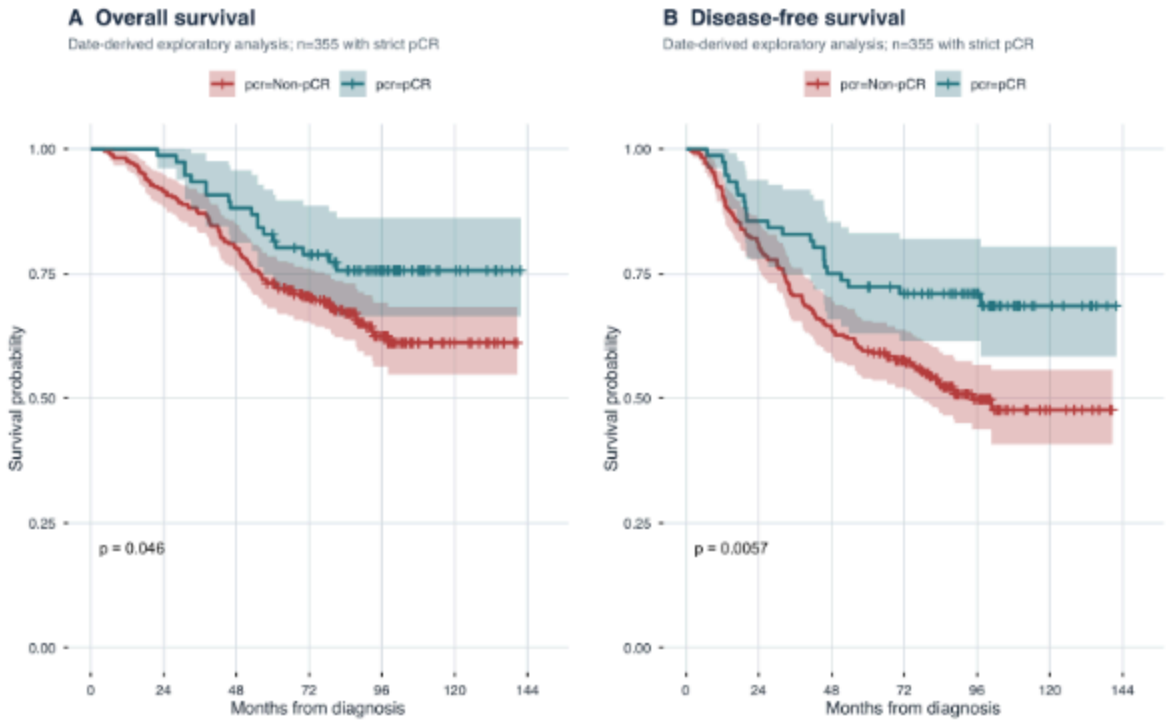


Figure 4

Date-based survival curves stratified by strictly defined pCR status. (A) Overall survival. (B) Disease-free survival. Curves, confidence bands, and censoring marks were derived from exploratory analyses reconstructed using registry date fields.

Supplementary Files

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