PS3-11-24

The Combined Immune-Stromal Score (CISS): A Novel Prognostic Gene Signature in Early ER-positive/HER2-positive Breast Cancer

Qiao Yang[1], Caroline Rönnlund[1,2], Caroline Schagerholm Stanev[1], Xinsong Chen[1], Theodoros Foukakis[1,3], Kang Wang[1], Irma Fredriksson[3–5], Stephanie Robertson[1], Emmanouil G. Sifakis[1] and Johan Hartman[1,2]

[1]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden, [2]Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden, [3]Breast Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden, [4]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, [5]Department of Breast-, Endocrine Tumors and Sarcoma, Karolinska University Hospital, Stockholm, Sweden.

San Antonio Breast Cancer Symposium - December 9–12 2025

INTRODUCTION

Background: Despite improved outcomes with combined Human Epidermal growth factor Receptor 2 (HER2) and estrogen receptor (ER)-targeted therapy, treatment resistance persists in ER-positive/HER2-positive breast cancer. While the roles of immune and stromal components are well-documented, their collective influence on clinical outcomes remains poorly understood.

Aim: We hypothesized that an integrated measurement of stromal–immune activity within the tumor-microenvironment (TME) could improve risk stratification for this disease.

MATERIALS & METHODS

Discovery Cohort (Stockholm HER2)

- **Patients:** 356 primary HER2-positive patients treated with adjuvant trastuzumab (Figure 1);
- **Profiling**: FFPE tumor analyzed using the NanoString BC360 panel;
- **Endpoint**: Recurrence-free survival (RFS), with a median follow-up of 8.8 years.

TME & CISS Derivation

- **Unsupervised clustering** revealed four distinct tumor-microenvironment (TME) states (Figure 2).
- The **Combined Immune-Stromal Score (CISS)** was derived a priori from 101 predefined immune/stromal genes using single-sample GSEA (ssGSEA) calculation.

Survival Analysis

- **Metric:** Hazard ratios (HR) are reported per 1-standard deviation (SD) increase in CISS.
- **Multivariable Cox models**:
  - Model 1: Adjusted for nodal status, tumor size, and stratified by ER status.
  - Model 2: Adjusted for nodal status and tumor size.

Primary Finding & Validation

- **Primary analysis:** In ER-positive/HER2-positive stockholm HER2 subset, a higher CISS was significantly associations with improved RFS by Model 1 (Figure 3a).
- **Multi-cohort validation**: CISS was validated in four independent cohorts (SCAN-B, METABRIC, TCGA, randomized neoadjuvant PREDIX-HER2) profiled across multiple platforms (RNA-seq, microarray, nCounter), using RFS/RFi/PFI as available endpoints (Model 2, Figure 3b).



Figure 1. Methods overview

RESULTS

TME states

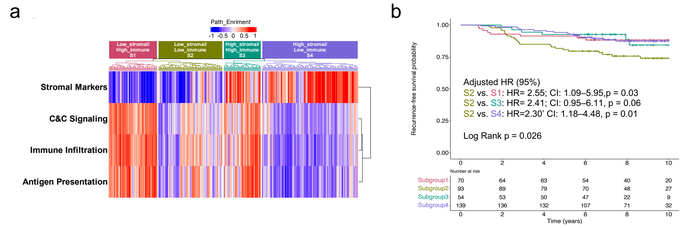


Figure 2. A low stromal/low immune subgroup (S2) has a poor outcome.
(a) Unsupervised clustering reveals four distinct TME states(S1-S4).
(b) The S2 subgroup is associated with significantly worse recurrence-free survival.

Clinicopathological associations of CISS

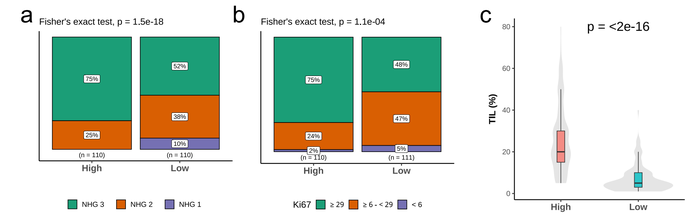


Figure 4. Association of CISS with clinical features in Stockholm HER2 subset.
CISS subgroups (High vs. Low) were analyzed for associations with (a) Nottingham histological grade, (b) categorical Ki67 (Fisher's exact tests) and (c) continuous TILs (Wilcoxon tests).

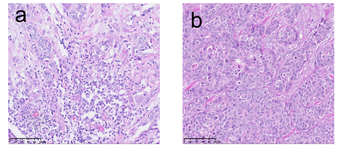


Figure 5. Association of CISS with pathological features in Stockholm HER2 subset.
Representative H&E images of (a) high- and (b) low-CISS tumors (scale bar: 100μm).

Prognostic impact of CISS

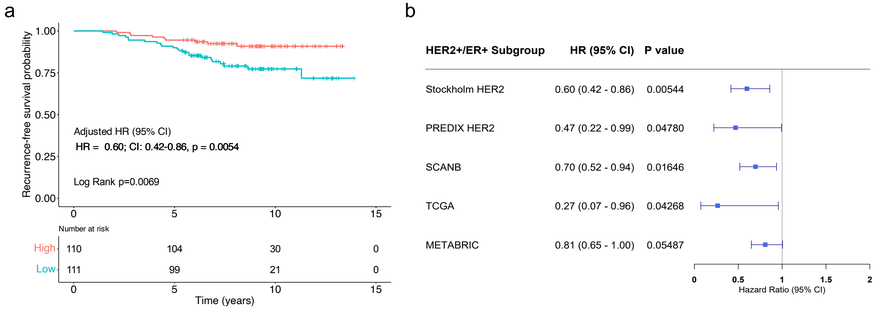


Figure 3. Prognostic implication of the CISS and its validation.
(a) Kaplan–Meier analysis in the discovery cohort shows that the high CISS (dichotomized by the median of CISS) is associated with significantly better recurrence-free survival (model 1).
(b) Forest plot confirms the consistent prognostic value of CISS (per 1-SD increase) in four independent validation cohorts (model 2)

CONCLUSION

Novel prognostic signature: CISS quantifies the integrated influence of the immune and stromal components of the tumor microenvironment.
Clinical implication: It consistently stratifies recurrence risk in early ER-positive/HER2-positive breast cancer across diverse cohorts and platforms.
Future direction: Prospective validation and decision-impact studies are warranted to assess whether CISS can guide risk-adapted therapy.

Disclosures:
The presenter has no conflict of interest to declare.

Funding:
Region Stockholm; cancerfonden; Bröstcancerförbundet; Radiumhemmets Forskningsfonder; Svenska Sällskapet för Medicinsk Forskning; China Scholarship Council (QY); Erik och Majje Näsström (IF).



Qiao Yang
PhD student at Karolinska Institutet

Karolinska Institutet, Department of Oncology-Pathology
Visionsgatan 56, 171 76 Stockholm, Sweden
qiao.yang@ki.se, +46 724451180
www.hartmanlab.com

This presentation is the intellectual property of the author/presenter. Contact them at qiao.yang@ki.se for permission to reprint and/or distribute.