Real-world outcomes by Estrogen Receptor Expression Subgroups in Patients with HER2-negative Breast Cancer: A Population-based Cohort Study

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Introduction

Background: Estrogen receptor (ER) status is a critical biomarker in breast cancer. While high ER expression (≈100%) demonstrates better response to endocrine therapy and low ER expression (1-9%) resembles ER-negative disease, the clinical significance of intermediate ER expression (10-59%) remains poorly understood, with a lack of treatment consensus.

Objective: To define tumor characteristics, treatment patterns, and overall survival trends across ER-status groups, with a special focus on ER-mild (10-29%) and ER-moderate (30-59%) expression.

Study design & methods

Study cohort & data source

- A retrospective, population-based cohort of all women diagnosed with HER2-negative breast cancer (BC) in Sweden (Jan 2007 – Dec 2023), as detailed in Figure 1.
- Data source: Swedish National Breast Cancer Quality Register (NKBC), SCAN-B dataset.

Stratification & groups

- Patients are stratified by ER status into five groups:
  - **ER-zero (0%)**
  - **ER-low (1-9%)**
  - **ER-mild (10-29%)**
  - **ER-moderate (30-59%; ER-mod)**
  - **ER-high positive (60-100%; ER-high)**
- Groups were analyzed by ER status and postoperative treatment: Chemotherapy only [CTonly], Endocrine therapy only [ETonly], Both [CT+ET], and Neither [None]).

Survival analysis

- **Overall survival (OS):** Estimated using Kaplan–Meier method across ER-status groups.
- **Multivariable Cox Models: Model 1**: Adjusted for tumor stage and grade, age, diagnosis year, as well as chemotherapy, endocrine therapy, and radiotherapy. **Model 2**: Stratified by radiotherapy status and adjusted for tumor stage and grade, age, and diagnosis year.

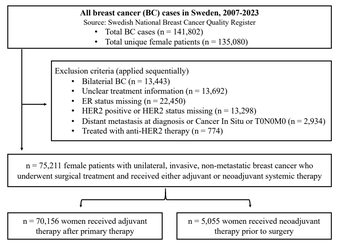


Figure 1. Patient selection flowchart

Results

OS by ER-status

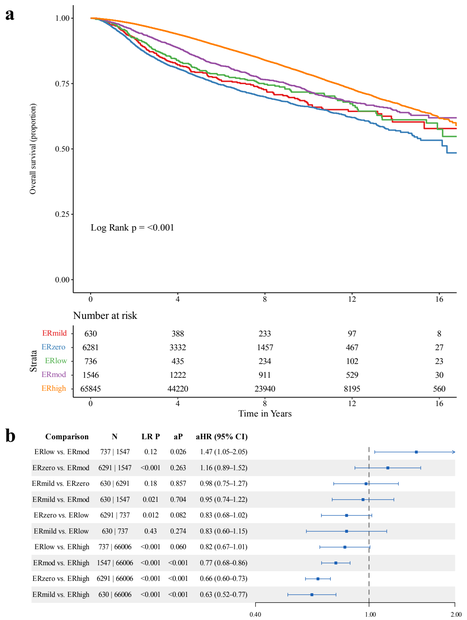


Figure 2. Overall survival by ER-status groups (n = 75, 211). (a) Kaplan-Meier survival curves. (b) Forest plot of adjusted hazard ratios (aHR) by model 1.

OS by treatment across ER-status

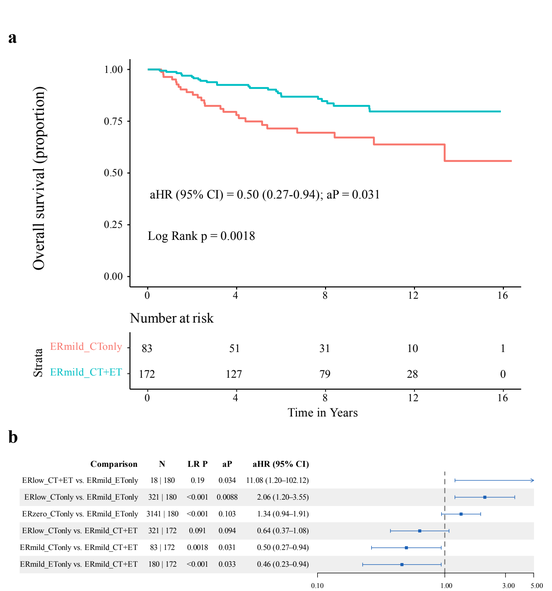


Figure 3. Multivariable Cox regression analysis by ER-status and postoperative treatment. (a) Kaplan-Meier survival curves. (b) Forest plot of aHR by model 2.

Molecular heterogeneity

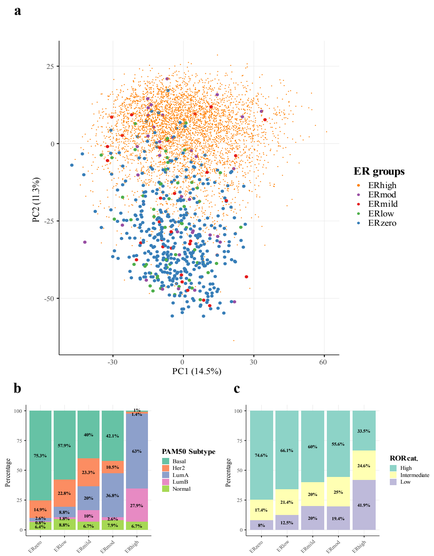


Figure 4. Molecular heterogeneity by ER-status. Transcriptomic analysis of the SCAN-B cohort (n = 4,767). (a) PCA plot of molecular profiles. (b) PAM50 intrinsic subtypes distribution. (c) Risk of recurrence (ROR) score categories (ROR cat.) distribution.

Summary

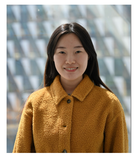
- **ER-mild & ER-low** tumors are clinically and molecularly similar to ER-zero.
- **Endocrine therapy benefit** is correlated with increasing ER percentage.
- **Molecular profiles** distinguish intermediate ER groups from ER-high tumors.

Clinical implication

- **ER status could be reported quantitatively**, to facilitate tailored treatment for intermediate ER (10-59%) patients.
- **GEP tests might be considered** for patients with ER intermediate tumors to guide optimal treatment decisions.

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