San Antonio Breast Cancer Symposium®, December 9-12, 2025

Association Between Peripheral Eosinophils and Survival Outcomes in HR+HER2- Breast Cancer: An Analysis of 15,262 Patients

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Background

Breast cancer exhibits complex immune regulation involving both the tumor microenvironment and systemic circulation. While lymphocyte-dominated immune responses in HR+HER2- breast cancer have been extensively investigated, the functional roles of granulocytic populations—particularly eosinophils—remain poorly understood, including their clinical relevance, tumor-immune interactions, and spatial organization.

Methods

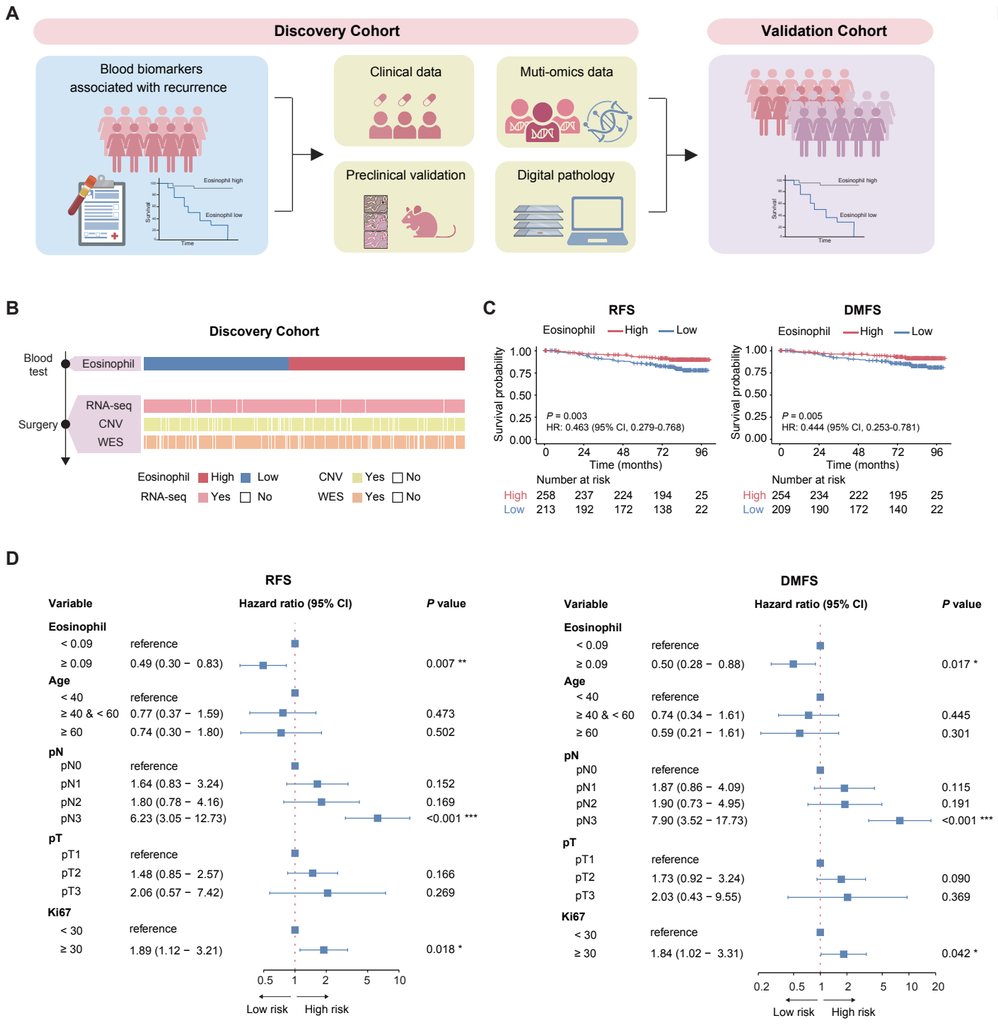
We analyzed a multi-omics discovery cohort (n=472) and a large clinical validation cohort (n=14,790) with matched preoperative peripheral eosinophil counts to assess their prognostic value in HR+HER2- breast cancer. Integrated analyses of whole-exome sequencing (WES), copy number alterations (CNAs) and RNA sequencing (RNA-seq) revealed distinct genomic and transcriptomic profiles between eosinophil-high and -low groups. The functional roles of eosinophils in tumor immunity were investigated through immunohistochemistry (IHC), adoptive transfer experiments, and flow cytometry analyses. Furthermore, we integrated IHC with digital pathology to map their spatial distribution in tumors.

Results

In both the discovery and validation cohorts, higher circulating eosinophil levels were associated with improved survival in HR+HER2- breast cancer. Genomic analysis revealed that higher circulating eosinophil levels were associated with lower HLA homozygosity. Circulating eosinophils were associated with increased intratumoral immune activation and more eosinophil infiltration within tumors. Tumors with high eosinophil infiltration exhibited significantly stronger anti-tumor immune responses. Mechanistically, eosinophils exerted anti-tumor effects through direct cytotoxicity and recruitment of $CD8^+$T cells, as evidenced by reduced tumor burden in eosinophil-adoptive transfer models. Spatial analysis using digital pathological profiling further suggested that tumor-infiltrating eosinophils were located closest to lymphocytes, followed by stromal cells and tumor cells.

Conclusions

Through integrative multi-omics analysis and spatial immune profiling, our study provides evidence for the anti-tumor role of eosinophils in HR+HER2- breast cancer. These findings establish eosinophils as a potential prognostic biomarker in this subtype, highlighting their relevance in the tumor immune microenvironment and potential utility in risk stratification.



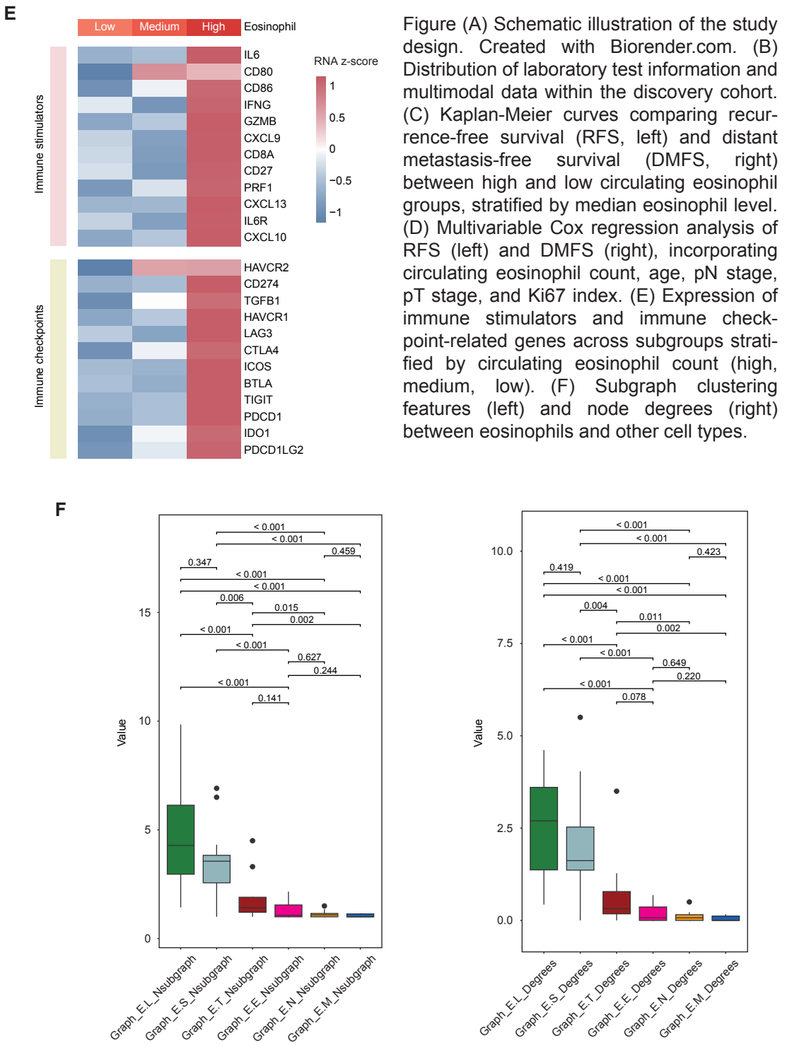


Figure (A) Schematic illustration of the study design. Created with Biorender.com. (B) Distribution of laboratory test information and multimodal data within the discovery cohort. (C) Kaplan-Meier curves comparing recurrence-free survival (RFS, left) and distant metastasis-free survival (DMFS, right) between high and low circulating eosinophil groups, stratified by median eosinophil level. (D) Multivariable Cox regression analysis of RFS (left) and DMFS (right), incorporating circulating eosinophil count, age, pN stage, pT stage, and Ki67 index. (E) Expression of immune stimulators and immune checkpoint-related genes across subgroups stratified by circulating eosinophil count (high, medium, low). (F) Subgraph clustering features (left) and node degrees (right) between eosinophils and other cell types.

Presentation Number: PS2-08-23

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