Letter to the Editor

Eur J Breast Health 2026; 22(1): 112-113
DOI: 10.4274/ejbh.galenos.2025.2025-6-7

Comment on "Prognostic Importance of PTEN and P53 in Aggressive Luminal A Subtype Breast Cancers"

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Cite this article as: Sah R. Comment on "prognostic importance of PTEN and P53 in aggressive luminal A subtype breast cancers". Eur J Breast Health. 2026; 22(1): 112-113

Dear Editor,

We read with great interest the study by Gemci et al. (1), which investigated the prognostic significance of phosphatase and tensin homolog (PTEN) and tumor protein p53 (p53) in aggressive Luminal A (LumA) subtype breast cancers. While the study attempted to identify histopathological predictors in a subtype generally associated with favorable outcomes, several analytical limitations require critical examination.

The classification of "aggressive LumA" based solely on recurrence or metastasis within five years, introduces the risk of misclassification due to the absence of genomic validation. Although molecular testing is not always available in clinical settings, reliance on immunohistochemical surrogates lacks the granularity provided by gene expression assays such as prediction analysis of microarray 50 (2). Notably, four of the five recurrent LumA cases exhibited features such as multifocality, lobular carcinoma *in situ*, or extensive intraductal component, which are known to confound subtype designation and may mimic LumA phenotypes despite underlying biological divergence (3).

Second, while all five recurrent LumA tumors showed low PTEN immunoreactivity score (<6), the comparison with non-recurrent LumA tumors failed to achieve statistical significance. The high overall prevalence of PTEN loss in the cohort (77.1%) limits its specificity, and no molecular confirmation through PTEN sequencing or methylation analysis was performed. These constraints diminish the ability to infer PTEN's prognostic independence.

Third, the interpretation of p53 histoscore (H-score) lacks biological validation. Assigning H-scores <10 as null-type p53 expression is inaccurate; such low scores can still reflect wild-type expression unless confirmed with sequencing. The threshold of <50 was used without genomic correlation, and most recurrent LumA tumors had H-scores <10. However, immunohistochemistry alone is insufficient to distinguish between wild-type, missense, and loss-of-function mutations (4). Without tumor protein p53 sequencing, these findings remain speculative.

In addition, tumor-infiltrating lymphocyte (TIL) density was evaluated using an arbitrary cutoff without reference to standardized scoring criteria, such as those proposed by the International Immuno-Oncology Biomarker Working Group. Although lower TIL density was observed in recurrent LumA tumors, the sample size of only five cases precludes robust inference. Moreover, the absence of multivariate modeling limits the ability to assess the independent contributions of each biomarker to recurrence risk (5).

In summary, while the study offers initial insight into the pathological features of aggressive LumA subtype breast cancers, the small sample size, absence of genomic validation, and non-standardized biomarker thresholds limit the reliability of its prognostic claims. Future work should incorporate multivariate analysis and molecular subtyping to establish the independent prognostic utility of PTEN and p53.

Footnotes

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declare that they received no financial support for this study.

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Received: 10.06.2025
Accepted: 15.07.2025
Epub: 04.09.2025
Online Publication Date: 25.12.2025

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