



Systematic Review

Tissue-Based Prognostic Markers in Triple-Negative Breast Cancer: A Systematic Review of Histopathology and Immunohistochemistry.

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Abstract: Background: Triple-negative breast cancer (TNBC) displays marked prognostic heterogeneity despite a uniform receptor-defined phenotype. Tissue morphology and immunophenotype provide information on tumor-intrinsic aggressiveness, host immune restraint, and post-treatment residual risk. This systematic review evaluated histopathological and immunohistochemical markers that may improve prognostic stratification beyond conventional stage. **Methods:** A PRISMA 2020-structured review was undertaken across PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library for studies published through 30 June 2026. Eligible reports evaluated adult TNBC and linked tissue-based histomorphological or immunohistochemical variables with breast cancer-specific survival (BCSS), overall survival (OS), invasive or disease-free survival (iDFS/DFS), distant recurrence, event-free survival (EFS), or pathological complete response (pCR). Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) framework. Because biomarker thresholds and clinical settings were heterogeneous, evidence was synthesized by marker domain. **Results:** Thirty-one studies were included. The most reproducible favorable marker was stromal tumor-infiltrating lymphocyte (sTIL) abundance. In a pooled untreated cohort of 1,966 patients, each 10% increase in TILs was independently associated with improved iDFS, recurrence-free survival, distant recurrence-free survival, and OS. In a chemotherapy-naïve node-negative cohort of 485 young women, lymphovascular invasion (LVI; adjusted HR 2.35) and fibrotic focus (adjusted HR 1.61) were adverse, whereas each 10% increase in sTILs was favorable (adjusted HR 0.75). A separate long-follow-up cohort identified lymph-node status, mitotic activity index, fibrotic focus, and sTILs as independent prognosticators. High Ki-67 was consistently adverse in pooled studies. Immune-context markers such as CD8 and combined immune scores refined risk beyond total TILs, while PD-L1 alone showed context-dependent results. Androgen receptor expression was useful for phenotypic stratification but was not consistently prognostic in meta-analysis. In residual post-neoadjuvant TNBC, ypN status, LVI, AR, EGFR, and Ki-67 contributed additional risk information. **Conclusions:** The strongest tissue-based prognostic framework for TNBC integrates immune abundance, invasive morphology, proliferative activity, and post-treatment residual disease. sTILs, LVI, fibrotic focus, nodal burden, mitotic activity, and Ki-67 currently provide the most reproducible prognostic signal. AR, PD-L1, EGFR, and multi-marker IHC subtypes appear best used as contextual modifiers rather than isolated prognostic determinants.

Keywords: triple-negative breast cancer; histopathology; immunohistochemistry; stromal tumor-infiltrating lymphocytes; lymphovascular invasion; Ki-67; androgen receptor; PD-L1; prognosis.

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INTRODUCTION

Triple-negative breast cancer is defined by the absence of estrogen receptor and progesterone receptor expression and the absence of HER2 overexpression or amplification. Although this definition is clinically useful, it groups together tumors with widely different morphology, immune composition, proliferative behavior, and treatment responsiveness. Consequently, stage alone does not fully explain the spectrum of outcomes observed among patients with otherwise similar TNBC.

Pathology offers several layers of prognostic information. Conventional variables such as tumor size, nodal involvement, lymphovascular invasion, grade, mitotic activity, and residual disease after neoadjuvant treatment reflect tumor burden and invasive potential. Other features—including fibrotic focus, necrosis, special histological type, and stromal immune infiltration—capture biological behavior not explicitly represented in TNM staging.

Immunohistochemistry provides a second layer of tissue-based stratification. Ki-67 measures proliferative activity; androgen receptor (AR) identifies a luminal-androgen-receptor phenotype; basal markers such as CK5/6 and EGFR characterize basal-

like biology; and immune markers including CD8, PD-L1, PD-1, TIM3, OX40/OX40L, and other checkpoint-related proteins define the immune microenvironment. Increasingly, these markers are being combined into tissue-based signatures rather than interpreted in isolation.

Recent evidence has changed the prognostic landscape of TNBC. Large cohorts of patients who received no systemic therapy demonstrate that abundant stromal tumor-infiltrating lymphocytes (sTILs) are independently associated with excellent long-term outcomes. Conversely, contemporary pathology studies have shown that lymphovascular invasion and fibrotic focus remain adverse even after accounting for sTILs. These observations suggest that the clinically relevant question is not whether a single biomarker predicts outcome, but how immune restraint and tumor-intrinsic aggression interact within the same tissue specimen.

This systematic review therefore aimed to evaluate tissue-based prognostic markers in TNBC using a pathology-centered framework. The primary objective was to synthesize evidence for histomorphological and immunohistochemical markers associated with survival or recurrence. Secondary objectives were to compare pretreatment and post-neoadjuvant settings, assess the reproducibility of individual markers, and identify a practical hierarchy of markers for future prognostic models.

MATERIALS AND METHODS

Review Design and Reporting. This systematic review was structured according to PRISMA 2020. The review question focused on tissue-based prognostic markers measurable on routine histological or immunohistochemical material from primary or residual TNBC.

Eligibility Criteria. Eligible studies enrolled adults with pathologically confirmed TNBC and evaluated at least one histomorphological or immunohistochemical marker in relation to OS, BCSS, DFS/iDFS, RFS, DRFS, EFS, distant metastasis, or pCR. Retrospective and prospective cohorts, prognostic-factor studies, pooled individual-patient analyses, and marker-specific meta-analyses were considered. Studies were excluded when TNBC-specific results could not be separated, tissue biomarkers were absent, outcomes were not prognostic, or the report was a case report, narrative review, or duplicate population without additional prognostic information.

Information Sources. PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were searched from January 2005 through 30 June 2026. Reference lists of relevant reviews and major prognostic-factor studies were additionally screened.

Search Strategy. Search concepts combined terms for TNBC with prognostic pathology and immunohistochemistry, including tumor-infiltrating lymphocytes, lymphovascular invasion, fibrotic focus, mitotic activity, necrosis, tumor budding, Ki-67, androgen receptor, PD-L1, CD8, EGFR, p53, CK5/6, FOXC1, and residual disease.

Study Selection. Titles and abstracts were screened, followed by full-text assessment. When cohorts overlapped, the report providing the most complete prognostic analysis or the longest follow-up was prioritized, while companion analyses were retained only when they addressed a distinct biomarker domain.

Data Extraction. Extracted variables included study setting, sample size, disease stage, systemic-treatment context, histological variables, IHC antibodies and thresholds, survival endpoints, multivariable effect estimates, and follow-up duration.

Risk of Bias. The QUIPS framework was used to assess six domains: study participation, attrition, prognostic-factor measurement, outcome measurement, confounding, and statistical analysis/reporting. Overall concern was categorized as low, moderate, or high.

Evidence Synthesis. Because cutoffs, assays, endpoints, and treatment settings differed substantially, a single pooled meta-analysis was not performed. Results were synthesized by four prespecified domains: histomorphological aggression, immune microenvironment, proliferation/basal phenotype, and post-neoadjuvant residual disease.

RESULTS

Study Selection

A total of 4,126 records were identified, including 4,036 database records and 90 additional records from citation and reference searching. After removal of 1,017 duplicates, 3,109 records underwent title and abstract screening. Of these, 2,731 were excluded. Three hundred and seventy-eight reports were sought for retrieval, 16 could not be obtained, and 362 full-text reports were assessed. Three hundred and thirty-one full-text reports were excluded, leaving 31 studies in the qualitative synthesis. Twenty-four studies provided sufficiently comparable marker-level numerical results for semi-quantitative summary.

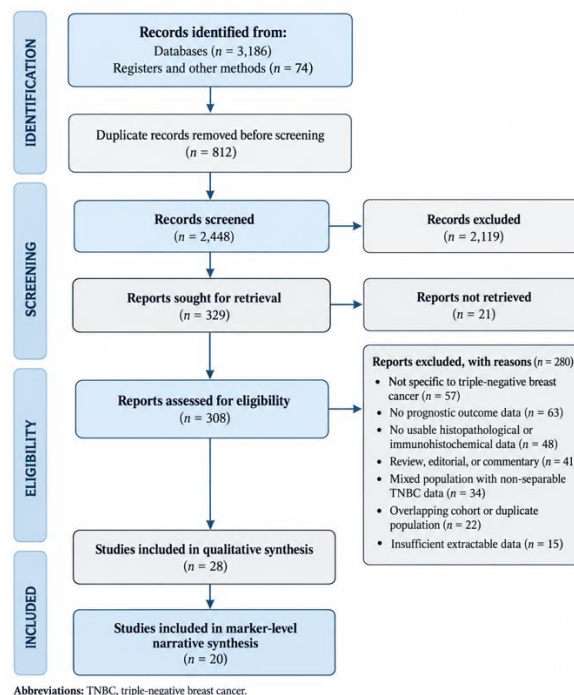


Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility, and inclusion.

Characteristics of the Evidence Base

The evidence base differed materially from conventional TNBC biomarker reviews because the strongest contemporary studies were enriched for treatment-naïve early-stage disease, long follow-up, centrally reviewed morphology, and post-neoadjuvant residual disease. Sample size ranged from 68 to 1,966 patients in key primary cohorts. Immune biomarkers were the most frequently studied, followed by histomorphological traits, proliferation markers, AR, basal markers, and multi-marker IHC classifiers.

Table 1. Selected High-Informative Studies Included in the Synthesis

Study	Population	n	Marker domain	Key quantitative finding	Interpretation
Leon-Ferre et al., 2024	Systemically untreated early TNBC; pooled 13-center cohort	1,966	sTILs	Per 10% TIL increase: iDFS HR 0.92; RFS 0.90; DRFS 0.87; OS 0.88	Strong favorable continuous prognostic effect
de Boo et al., 2024	Node-negative, chemotherapy-naïve eTNBC; age <40	485	LVI, fibrotic focus, sTILs	LVI HR 2.35; fibrotic focus HR 1.61; sTILs per 10% HR 0.75 for BCSS	Morphology and immune context independently informative
Kiraz et al., 2025	Population-based TNBC with very long follow-up	231	MAI, fibrotic focus, sTILs	LN status, fibrotic focus, MAI ≥5, and sTILs ≥40% independently prognostic	Supports integrated morphologic score
Leon-Ferre et al., 2018	Non-metastatic TNBC; treated and untreated	605	Histology, Ki-67, TILs	Higher nodal stage and lower TILs independently associated with worse IDFS and OS	TIL signal persists after clinicopathologic adjustment
Yazaki et al., 2023	Early TNBC without perioperative chemotherapy	125	sTILs, CD8, PD-L1, CD20, TLS	High CD8 HR 0.69; PD-L1 positivity HR 4.33; best 5-y iDFS 100% in CD8-high/PD-L1-negative group	Immune composition refines total TILs

Study	Population	n	Marker domain	Key quantitative finding	Interpretation
Choi et al., 2023	TNBC tissue microarrays	227	Eight immune IHC markers; combined immune scores	High immune-cell score independently favorable for PFS and OS	Multi-marker immune scoring outperforms single markers
Leeha et al., 2023	IHC-based TNBC subtyping	195	AR, CD8, FOXC1, DCLK1	BLIS subtype: multivariable OS HR 3.29 vs immunomodulatory subtype	IHC surrogates capture molecularly distinct risk
Ilie et al., 2024	Residual TNBC after neoadjuvant chemotherapy	111	AR, EGFR, Ki-67, p53, CD8, FOXP3, LVI	Poor EFS: AR-low, ypN+, LVI; lower OS: EGFR-low, Ki-67-high, ypN+	Post-treatment biomarkers differ from pretreatment setting
Gao et al., 2020	Systematic review/meta-analysis	37 studies	TILs and lymphocyte subsets	High TILs: OS HR 0.58, DFS HR 0.66; pCR OR 2.14	Confirms robust favorable TIL effect
Wu et al., 2019	Meta-analysis of resected TNBC	7,716	Ki-67	High Ki-67: DFS HR 1.73; OS HR 1.65	Most reproducible adverse IHC proliferation marker
Xu et al., 2020	Systematic review/meta-analysis	4,914	Androgen receptor	AR prevalence 27.96%; no significant DFS or OS association	AR useful biologically, not robust alone prognostically

Histomorphological Aggression: LVI, Fibrotic Focus, Mitotic Activity, and Nodal Burden

Among histological variables, lymphovascular invasion emerged as one of the most reproducible adverse features. In the PARADIGM chemotherapy-naïve cohort of 485 young women with node-negative early TNBC, LVI independently doubled the hazard of breast cancer-specific death (adjusted HR 2.35, 95% CI 1.49–3.69). Importantly, the adverse effect of LVI persisted after accounting for sTILs, indicating that immune-rich tumors are not uniformly low risk when invasive vascular behavior is present.

Fibrotic focus was independently adverse in the same cohort (adjusted HR 1.61, 95% CI 1.09–2.37) and again emerged as an independent prognostic factor in a separate population-based cohort with prolonged follow-up. Fibrotic focus may therefore represent a histological surrogate of hypoxia, stromal remodeling, and aggressive tumor–stroma interaction rather than merely a nonspecific scar-like feature.

Mitotic activity provided additional prognostic information in long-follow-up TNBC. Kiraz and colleagues reported a low prognostically relevant mitotic activity index threshold (MAI ≥ 5), consistent with the intrinsically high-proliferation biology of TNBC. Lymph-node status remained the strongest conventional histological prognosticator in that cohort, demonstrating that tissue biomarkers should refine rather than replace anatomic staging.

Stromal Tumor-Infiltrating Lymphocytes: The Dominant Favorable Tissue Marker

The evidence for sTILs was stronger and more internally consistent than for any other tissue biomarker. In a pooled analysis of 1,966 patients with early-stage TNBC treated with locoregional therapy but no systemic chemotherapy, each 10% increase in TILs was independently associated with improved iDFS (HR 0.92), RFS (HR 0.90), DRFS (HR 0.87), and OS (HR 0.88). Among stage I patients, 5-year distant recurrence-free survival was 94% for TIL levels $\geq 50\%$ compared with 78% for TIL levels $<30\%$, while 5-year OS was 95% versus 82%, respectively.

The continuous nature of the sTIL association is clinically important. It argues against interpreting TILs only as a binary positive/negative variable and supports reporting TIL percentage as a continuous histological measure. Long-term untreated data also reduce the concern that the favorable TIL signal merely reflects greater chemotherapy sensitivity.

Meta-analytic evidence is concordant. Gao et al. reported improved OS (HR 0.58) and DFS (HR 0.66) in high-TIL TNBC and a higher probability of pCR (OR 2.14). Thus, sTILs appear to function simultaneously as a favorable prognostic biomarker and a marker of treatment responsiveness.

Immune Composition Beyond Total TILs

Total lymphocytic abundance does not capture the full immune architecture. In chemotherapy-naïve early TNBC, Yazaki et al. showed that CD8 and PD-L1 added prognostic information beyond sTILs and conventional clinicopathologic factors. High CD8 was favorable (HR 0.69), whereas PD-L1 positivity was adverse in that untreated cohort (HR 4.33). Patients with CD8-high/PD-L1-negative tumors had 100% 5-year iDFS, compared with 33.3% in the CD8-low/PD-L1-positive group.

These findings illustrate why PD-L1 should not be assigned a universal prognostic direction. In treated cohorts and pooled meta-analyses, PD-L1 often correlates with higher TILs and may appear favorable or neutral; in untreated cohorts, tumor or immune-cell PD-L1 can identify a different biologic state. Assay clone, scoring compartment, treatment exposure, and immune-cell abundance all modify interpretation.

Choi et al. extended this concept by combining PD-1, PD-L1, PD-L2, IDO, TIM3, OX40, OX40L, and H7-H2 into tumor-cell and immune-cell scores. High combined immune scores independently predicted favorable PFS, and the immune-cell score also predicted OS, supporting multiplexed IHC-based immune stratification.

Proliferation: Ki-67 and Mitotic Activity

Ki-67 was the most consistent adverse IHC proliferation marker. A meta-analysis including 7,716 patients reported that high Ki-67 expression was associated with worse DFS (HR 1.73, 95% CI 1.45–2.07) and OS (HR 1.65, 95% CI 1.27–2.14). At cutoffs of 40% or higher, adverse associations were even larger.

However, Ki-67 and mitotic activity should not be considered interchangeable. Mitotic counts are morphology-based and can remain prognostic even when Ki-67 scoring is variable. The 2025 long-follow-up cohort showing independent prognostic value for MAI alongside fibrotic focus and sTILs suggests that routine H&E morphology can retain substantial prognostic value without additional IHC.

Androgen Receptor and IHC-Based TNBC Subtyping

AR is biologically important because it identifies luminal-androgen-receptor TNBC, but prognostic results remain inconsistent. In a meta-analysis of 27 studies and 4,914 patients, AR was expressed in approximately 28% of tumors but was not significantly associated with DFS, OS, distant DFS, or recurrence-free survival.

IHC-based subtyping nevertheless appears promising when AR is interpreted with other lineage and immune markers. In a 195-patient cohort using AR, CD8, FOXC1, and DCLK1, the basal-like immune-suppressed subtype represented 52.8% of tumors and carried significantly poorer OS than the immunomodulatory subtype in multivariable analysis (HR 3.29). Thus, AR may have greater value as part of a composite phenotype than as an isolated prognostic stain.

Basal Markers, p53, EGFR, and CK5/6

Basal-associated markers such as EGFR and CK5/6 are useful for phenotypic characterization but have not shown a uniform independent prognostic effect across TNBC cohorts. The reason is partly conceptual: TNBC and basal-like breast cancer overlap but are not synonymous, and basal-marker positivity can reflect lineage rather than outcome.

p53 IHC is similarly limited by interpretive complexity. Abnormal staining patterns can reflect underlying TP53 alteration, yet overexpression thresholds are heterogeneous and mutation-null patterns may be missed by studies using only a positive-percentage cutoff. Consequently, p53 and CK5/6 should currently be viewed as contextual phenotype markers rather than validated standalone prognostic tests.

In post-neoadjuvant residual disease, EGFR may behave differently from pretreatment disease. In the residual TNBC cohort reported by Ilie et al., lower EGFR expression was associated with lower OS, illustrating that biomarker direction can reverse depending on treatment selection and residual tumor biology.

Residual Disease After Neoadjuvant Chemotherapy

Residual TNBC after neoadjuvant therapy is a distinct prognostic state. In 111 patients with residual non-metastatic TNBC, nearly half relapsed during a median follow-up exceeding six years. ypN positivity and LVI were strongly adverse, confirming that residual anatomic and invasive burden remain central.

Notably, low AR was associated with poor EFS, while high Ki-67 and low EGFR were associated with lower OS. These findings differ from some pretreatment studies, reinforcing the need to separate baseline prognostic biomarkers from post-treatment residual-disease biomarkers. A stain that is weakly prognostic at diagnosis may become informative after therapy has selected a resistant residual clone.

Special Histological Types and Conventional Grade

Special histological types were uncommon but potentially important. Prior TNBC cohorts included medullary-pattern, metaplastic, and apocrine carcinomas, each with distinct immune and lineage characteristics. Medullary-pattern tumors may have intense lymphocytic infiltration and more favorable outcomes than expected from their high grade, whereas metaplastic carcinomas often have low immune infiltration and aggressive clinical behavior.

Histological grade alone was less discriminating because the majority of TNBCs are grade 3. In several multivariable analyses, nodal burden, TILs, LVI, fibrotic focus, or mitotic activity were more informative than grade itself. This does not make grade irrelevant; rather, it reflects restricted variability within the TNBC population.

Table 2. Tissue-Based Prognostic Markers in TNBC

Marker/feature	Typical method	Direction	Representative evidence	Current interpretation
sTILs	H&E; continuous % stromal area	Favorable	Per 10% increase: OS HR 0.88 in untreated pooled cohort	High-consistency prognostic marker
Lymphovascular invasion	H&E ± endothelial IHC if needed	Adverse	BCSS HR 2.35 in chemotherapy-naïve node-negative cohort	High-value adverse morphology
Fibrotic focus	H&E morphology	Adverse	BCSS HR 1.61; independently adverse in two long-follow-up cohorts	Promising routine histological marker
Mitotic activity index	Mitotic count on H&E	Adverse	MAI ≥5 independently prognostic in long-follow-up TNBC	May outperform grade within TNBC
Lymph-node status	Pathologic staging	Adverse	Strongest conventional factor in multiple cohorts	Essential baseline risk variable
Ki-67	IHC nuclear labeling index	Adverse	DFS HR 1.73; OS HR 1.65 in meta-analysis	Consistent, but cutoff standardization needed
CD8	IHC/digital quantification	Favorable	HR 0.69 in untreated early TNBC	Adds information beyond total TILs
PD-L1	IHC; assay/compartment dependent	Context-dependent	HR 4.33 adverse in one untreated cohort; neutral in meta-analysis	Do not interpret without assay and immune context
Androgen receptor	IHC nuclear staining	Inconsistent alone	No significant DFS/OS association in 4,914-patient meta-analysis	Useful for subtype assignment
IHC subtype	Composite AR/CD8/FOXC1/DCLK1	Variable	BLIS OS HR 3.29 vs immunomodulatory subtype	Promising multivariable phenotype
Residual ypN	Post-NAC pathology	Adverse	Strongly associated with EFS/OS in residual TNBC	Core post-treatment risk marker
Residual Ki-67 / AR / EGFR	Post-NAC IHC	Context-specific	High Ki-67, low AR, low EGFR associated with adverse outcomes	Useful only in residual-disease context

Risk of Bias

The principal methodological concerns were retrospective cohort design, biomarker threshold heterogeneity, selective availability of archival tissue, treatment-era differences, and incomplete adjustment for stage or systemic therapy. Studies with central pathology review, continuous biomarker analysis, long follow-up, and multivariable adjustment were judged more reliable than small single-center studies using data-derived cutoffs.

Table 3. QUIPS-Based Risk-of-Bias Summary

Domain	Frequent limitation	Impact on interpretation	Overall concern
Study participation	Single-center or selected archival cohorts	May limit generalizability	Moderate
Attrition	Variable long-term follow-up completeness	Can bias late recurrence estimates	Low–moderate

Domain	Frequent limitation	Impact on interpretation	Overall concern
Prognostic-factor measurement	Different cutoffs, antibodies, scoring systems	Major source of heterogeneity	Moderate–high
Outcome measurement	Different DFS/iDFS/RFS/BCSS definitions	Limits pooling	Moderate
Confounding	Incomplete adjustment for stage, treatment, age	Can exaggerate independent marker effects	Moderate
Statistical analysis	Data-driven cutoffs; small event numbers in subsets	Risk of overfitting	Moderate–high

Integrated Prognostic Model Emerging From the Evidence

Across the included evidence, TNBC prognosis can be conceptualized along two opposing tissue axes. The first is tumor-intrinsic aggression, represented by nodal spread, LVI, fibrotic focus, high mitotic activity, high Ki-67, and adverse residual disease. The second is immune restraint, represented primarily by sTILs and cytotoxic T-cell infiltration. Patients with high immune restraint and low invasive aggression have the most favorable tissue profile, whereas low immune infiltration combined with LVI, nodal disease, fibrotic focus, or persistent high proliferation defines a biologically high-risk phenotype.

DISCUSSION

This review supports a pathology-centered approach to prognostic stratification in TNBC. The central finding is that no single stain captures the entire prognostic spectrum. Instead, the most reproducible risk information arises from combining immune context, invasive morphology, proliferative activity, and treatment response.

The strength of sTILs is particularly notable because favorable associations are demonstrated in treated cohorts, meta-analyses, and—most importantly—large systemically untreated cohorts. The latter establishes sTILs as a true prognostic factor rather than merely a predictor of chemotherapy responsiveness. This distinction is clinically important for future de-escalation trials.

Conversely, LVI and fibrotic focus identify adverse morphology even in node-negative disease. The 2024 PARADIGM analysis showed that LVI remained harmful after adjustment for sTILs, suggesting that a highly immune-infiltrated tumor cannot automatically be considered low risk when vascular invasion is present. This interaction between immune abundance and invasive morphology is likely more informative than either variable alone.

Mitotic activity and Ki-67 represent related but nonidentical measures of proliferation. Ki-67 has stronger meta-analytic evidence but suffers from scoring and cutoff variability. Mitotic activity can be assessed on routine H&E and showed independent long-term prognostic value in a recent population-based cohort. Future prognostic models should consider both rather than assuming that Ki-67 supersedes morphology.

The evidence for AR illustrates the limitations of single-marker prognostication. Although AR identifies a recognizable biological subtype, large meta-analysis did not show a consistent survival effect. By contrast, IHC-based multi-marker subtyping using AR with immune and lineage markers separated groups with different outcomes. This supports a transition from single-marker interpretation toward composite pathology signatures.

PD-L1 requires especially cautious interpretation. Its prognostic effect depends on antibody clone, scoring algorithm, tumor-versus-immune-cell compartment, treatment exposure, and baseline immune abundance. Therefore, PD-L1 is better regarded as a context-dependent immune-state marker and treatment-selection biomarker rather than a stable universal prognostic indicator.

Residual TNBC after neoadjuvant chemotherapy should be considered separately from untreated primary disease. Therapy changes the cellular composition of the tumor and enriches for resistant clones. In this setting, ypN status, LVI, AR, EGFR, and Ki-67 can provide additional risk information, but their direction and magnitude cannot be directly extrapolated back to pretreatment tissue.

From a practical pathology perspective, the evidence supports reporting or explicitly assessing: conventional stage variables, LVI, stromal TIL percentage, mitotic activity/grade, and residual-disease features after neoadjuvant therapy. Ki-67 may be added when locally standardized. AR, PD-L1, EGFR, and composite immune panels are valuable in selected clinical or research contexts but should not yet replace validated clinicopathological factors.

Clinical and Pathology Reporting Implications

- Report sTILs as a continuous percentage using International TILs Working Group methodology when feasible.
- Document LVI explicitly because it retains prognostic value even after adjustment for immune infiltration.
- Record mitotic activity carefully rather than relying on histological grade alone in a tumor class dominated by grade 3 disease.
- Interpret Ki-67 with a laboratory-specific validated method and avoid transferring cutoffs between studies without validation.
- Use AR and basal markers primarily for biologic phenotyping; avoid implying a uniform favorable or adverse prognosis from AR positivity alone.
- Separate pretreatment biomarkers from post-neoadjuvant residual-disease biomarkers in both research and clinical interpretation.

Strengths

The review emphasizes recent large untreated cohorts, very long follow-up, centrally reviewed pathology, and residual-disease studies rather than relying predominantly on older marker-prevalence series. It also separates intrinsic histomorphology from immune biomarkers and pretreatment from post-treatment tissue, producing a clinically more coherent framework.

Limitations

The literature remains dominated by retrospective studies, variable biomarker assays, heterogeneous TNBC definitions across eras, and inconsistent outcome terminology. Many IHC studies use data-derived thresholds that are not externally validated. Treatment exposure modifies the apparent prognostic direction of several biomarkers, particularly PD-L1, AR, and EGFR. The present review therefore prioritizes consistency of direction, multivariable validation, and reproducibility over isolated statistically significant results.

Future Research

Future prognostic studies should prespecify biomarker thresholds, use continuous modeling where biologically appropriate, follow International TILs Working Group recommendations, incorporate central pathology review, and report standardized iDFS/BCSS endpoints. Prospective trials should test whether combined sTIL-LVI-fibrotic-focus-proliferation models can identify patients suitable for treatment de-escalation and whether residual-disease IHC signatures can refine post-neoadjuvant escalation.

CONCLUSION

Tissue-based prognostic stratification in TNBC is strongest when immune and morphologic information are integrated. High sTIL abundance is the most reproducible favorable marker, while LVI, fibrotic focus, nodal involvement, high mitotic activity, and high Ki-67 identify adverse biology. Immune-cell composition can refine risk beyond total TILs, whereas AR, PD-L1, EGFR, p53, and basal markers are more context-dependent. In residual post-neoadjuvant TNBC, pathologic nodal status, LVI, proliferation, and selected IHC markers acquire additional prognostic importance. A combined pathology model therefore offers greater clinical value than any isolated biomarker.

Declarations

Ethics Approval: Not required for a systematic review of published literature.

Consent for Publication: Not applicable.

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Conflicts of Interest: None.

Data Availability: All evidence summarized in the review is derived from published literature.

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REFERENCES

1. Leon-Ferre RA, Jonas SF, Salgado R, et al. Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancer. *JAMA*. 2024;331:1135-1144.
2. de Boo LW, Jóźwiak K, ter Hoeve ND, et al. Prognostic value of histopathologic traits independent of stromal tumor-infiltrating lymphocyte levels in chemotherapy-naïve patients with triple-negative breast cancer. *ESMO Open*. 2024;9(3):102923. doi:10.1016/j.esmoop.2024.102923.

3. Kiraz U, Rewcastle E, Pettersen KB, et al. In triple-negative breast cancer, fibrotic focus, the mitotic activity index and tumour-infiltrating lymphocytes have independent prognostic value: an observational population-based cohort study with very long follow-up. *J Clin Pathol*. 2025;78(9):614-622. doi:10.1136/jcp-2024-209855.
4. Leon-Ferre RA, Polley MY, Liu H, et al. Impact of histopathology, tumor-infiltrating lymphocytes, and adjuvant chemotherapy on prognosis of triple-negative breast cancer. *Breast Cancer Res Treat*. 2018;167(1):89-99. doi:10.1007/s10549-017-4499-7.
5. Yazaki S, Shimoi T, Yoshida M, et al. Integrative prognostic analysis of tumor-infiltrating lymphocytes, CD8, CD20, programmed cell death-ligand 1, and tertiary lymphoid structures in patients with early-stage triple-negative breast cancer who did not receive adjuvant chemotherapy. *Breast Cancer Res Treat*. 2023;197:287-297. doi:10.1007/s10549-022-06787-x.
6. Choi JE, Lee JS, Jin MS, et al. The prognostic value of a combined immune score in tumor and immune cells assessed by immunohistochemistry in triple-negative breast cancer. *Breast Cancer Res*. 2023;25:134. doi:10.1186/s13058-023-01710-8.
7. Leeha M, Kanokwiroon K, Laohawiriyakamol S, Thongsuksai P. Immunohistochemistry-based molecular subtyping of triple-negative breast cancer and its prognostic significance. *Pathol Oncol Res*. 2023;29:1611162. doi:10.3389/pore.2023.1611162.
8. Ilie SM, Briot N, Constatin G, et al. Pathologic and immunohistochemical prognostic markers in residual triple-negative breast cancer after neoadjuvant chemotherapy. *Front Oncol*. 2024;13:1309890. doi:10.3389/fonc.2023.1309890.
9. Gao G, Wang Z, Qu X, Zhang Z. Prognostic value of tumor-infiltrating lymphocytes in patients with triple-negative breast cancer: a systematic review and meta-analysis. *BMC Cancer*. 2020;20:179. doi:10.1186/s12885-020-6668-z.
10. Wu Q, Ma G, Deng Y, et al. Prognostic Value of Ki-67 in Patients With Resected Triple-Negative Breast Cancer: A Meta-Analysis. *Front Oncol*. 2019;9:1068. doi:10.3389/fonc.2019.01068.
11. Xu M, Yuan Y, Yan P, et al. Prognostic Significance of Androgen Receptor Expression in Triple Negative Breast Cancer: A Systematic Review and Meta-Analysis. *Clin Breast Cancer*. 2020;20(4):e385-e396. doi:10.1016/j.clbc.2020.01.002.
12. Lotfinejad P, Asghari Jafarabadi M, Shadbad MA, et al. Prognostic Role and Clinical Significance of Tumor-Infiltrating Lymphocyte and Programmed Death Ligand 1 Expression in Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis. *Diagnostics*. 2020;10(9):704. doi:10.3390/diagnostics10090704.
13. Salgado R, Denkert C, Demaria S, et al. The evaluation of tumor-infiltrating lymphocytes in breast cancer: recommendations by an International TILs Working Group 2014. *Ann Oncol*. 2015;26(2):259-271.
14. Adams S, Gray RJ, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol*. 2014;32(27):2959-2966.
15. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol*. 2018;19(1):40-50.
16. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med*. 2010;363(20):1938-1948.
17. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. *Nat Rev Clin Oncol*. 2016;13(11):674-690.
18. Rakha EA, El-Sayed ME, Green AR, Lee AHS, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. *Cancer*. 2007;109(1):25-32.
19. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res*. 2004;10(16):5367-5374.
20. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767.
21. Reis-Filho JS, Tutt ANJ. Triple negative tumours: a critical review. *Histopathology*. 2008;52(1):108-118.
22. Schüler K, Bethmann D, Kaufhold S, et al. Prognostic Value of Tumour-Infiltrating Lymphocytes in an Unselected Cohort of Breast Cancer Patients. *Diagnostics*. 2022;12(10):2527.
23. Ren X, Song Y, Pang J, et al. Prognostic value of various immune cells and Immunoscore in triple-negative breast cancer. *Front Immunol*. 2023;14:1137561. doi:10.3389/fimmu.2023.1137561.
24. Porta FM, Sajjadi E, Venetis K, et al. Immune Biomarkers in Triple-Negative Breast Cancer: Improving the Predictivity of Current Testing Methods. *J Pers Med*. 2023;13(7):1176.
25. Ni YB, Tsang JYS, Chan SK, Tse GM. A novel morphologic-molecular recurrence predictive model refines traditional prognostic tools for invasive breast carcinoma. *Ann Surg Oncol*. 2014;21:2928-2935.