



Systematic Review

Pathology-Based Prognostic Stratification in Triple-Negative Breast Cancer: A Systematic Review of Morphological and Immunohistochemical Markers.

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Abstract: **Background:** Triple-negative breast cancer (TNBC) encompasses morphologically and immunophenotypically diverse carcinomas with markedly different risks of recurrence despite a shared ER-negative, PR-negative, and HER2-negative definition. This review evaluated conventional histomorphology together with immunohistochemical and immune-microenvironmental biomarkers that may refine prognostic stratification. **Methods:** A PRISMA 2020-oriented systematic review was structured across PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane CENTRAL, supplemented by citation searching. Adult TNBC studies reporting overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), distant recurrence, or neoadjuvant pathological response in relation to tissue-based biomarkers were eligible. Thirty-two studies were included in qualitative synthesis and 24 contributed marker-specific quantitative or semi-quantitative evidence. **Results:** The most reproducible favorable feature was a lymphocyte-rich tumor microenvironment. Meta-analytic estimates showed better OS and DFS with higher stromal tumor-infiltrating lymphocytes (STILs), while residual-disease TILs provided additional prognostic information beyond residual cancer burden (RCB). High Ki-67 consistently identified higher-risk disease, with pooled hazard ratios of 1.73 for DFS and 1.65 for OS in resected TNBC. PD-L1 positivity in non-metastatic TNBC was associated with greater pathological complete response (pCR) and, in selected datasets, improved survival, although assay and scoring heterogeneity remained substantial. Androgen receptor (AR) expression identified a biologically distinct subset but showed no consistent independent survival advantage across pooled analyses. A 2024 cohort further suggested that dual SOX10/AR negativity may mark an adverse immunophenotype. Morphological risk was concentrated in advanced pathological stage, nodal involvement, lymphovascular invasion (LVI), extensive residual disease, and high RCB class. **Conclusion:** Prognostic stratification in TNBC is strongest when conventional pathology is integrated with immune and proliferative biomarkers. STILs, Ki-67, residual cancer burden, LVI, and post-neoadjuvant residual disease features currently have the most consistent clinicopathological signal. AR, PD-L1, SOX10, EGFR, p53, and basal cytokeratins are informative but require context-specific interpretation and standardized assays before routine standalone prognostic use.

Keywords: triple-negative breast cancer; histomorphology; immunohistochemistry; prognosis; stromal tumor-infiltrating lymphocytes; Ki-67; androgen receptor; PD-L1; residual cancer burden.

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INTRODUCTION

Triple-negative breast cancer is defined clinically by the absence of estrogen receptor (ER) and progesterone receptor (PR) expression and by the absence of HER2 overexpression or amplification. Although this definition is therapeutically useful, it encompasses a heterogeneous group of carcinomas that differ substantially in morphology, immune composition, molecular phenotype, treatment response, and long-term outcome [1-4]. The practical consequence is that two tumors meeting identical receptor criteria may have very different patterns of relapse and survival.

Histopathology provides the first layer of risk stratification. Tumor size, nodal involvement, Nottingham grade, lymphovascular invasion, geographic necrosis, stromal composition, and post-treatment residual disease are visible manifestations of tumor biology. In the neoadjuvant setting, pathological complete response and residual cancer burden have become particularly important because they capture chemosensitivity and residual metastatic potential within a single pathological assessment [5,6].

A second layer of prognostic information comes from immunohistochemistry (IHC) and immune-microenvironmental assessment. Ki-67 reflects proliferative activity; androgen receptor (AR) helps identify luminal-androgen-receptor biology; SOX10, CK5/6, EGFR, and related markers highlight basal differentiation; PD-L1 informs the immune checkpoint axis; and p53 staining serves as an imperfect surrogate of TP53 pathway disruption. Stromal tumor-infiltrating lymphocytes (STILs), although assessed on routine H&E rather than strictly by IHC, have emerged as one of the most clinically mature immune biomarkers in TNBC [7-10].

The prognostic interpretation of these features is complicated by variability in antibodies, thresholds, scoring systems, treatment era, clinical stage, and whether tissue was collected before or after neoadjuvant systemic therapy. For example, AR-positive tumors may display lower proliferation but not necessarily superior survival, and PD-L1 may behave differently depending on whether tumor-cell or immune-cell staining is measured. Similarly, a high pretreatment TIL score and a high residual-disease TIL score do not have identical biological meaning.

This systematic review therefore focused on a pathology-centered question: which histomorphological and immunohistochemical biomarkers provide reproducible prognostic information in TNBC, and how should they be integrated with conventional stage and post-neoadjuvant response? The review also examined the limitations that currently prevent wider incorporation of promising biomarkers into routine prognostic reporting.

MATERIALS AND METHODS

Review Question and Eligibility Framework

The review question was: among adult patients with TNBC, which histomorphological and immunohistochemical tissue features are associated with prognosis or treatment-response outcomes? Eligible studies included primary TNBC cohorts, translational analyses embedded within clinical trials, and well-defined observational studies reporting tissue biomarkers in relation to OS, DFS, RFS, event-free survival, distant recurrence, or pathological response. Studies were excluded when TNBC data could not be separated from other breast cancer subtypes, when no prognostic outcome was reported, or when tissue biomarker methods were insufficiently described.

Information Sources and Search Strategy

The search framework covered PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane CENTRAL from January 2008 through 30 June 2026. Reference lists of relevant systematic reviews, meta-analyses, and pathology-focused TNBC articles were also examined. Search concepts combined "triple-negative breast cancer" or "TNBC" with terms for morphology, histology, lymphovascular invasion, necrosis, residual cancer burden, tumor-infiltrating lymphocytes, Ki-67, androgen receptor, PD-L1, SOX10, EGFR, CK5/6, p53, prognosis, survival, recurrence, and pathological complete response.

Outcomes

The primary outcomes were OS and DFS/RFS. Secondary outcomes included distant recurrence, pathological complete response, event-free survival, residual cancer burden class, and treatment-response measures when used as clinically validated prognostic surrogates. Biomarkers were categorized as histomorphological, immune-microenvironmental, proliferative, luminal/apocrine, basal, or checkpoint-related.

Study Selection and Data Extraction

Study selection was organized in sequential title/abstract and full-text stages. Extracted information included study design, cohort size, treatment setting, specimen timing, biomarker method, positivity threshold, pathological features, outcome definition, follow-up, effect estimates, and variables included in multivariable analysis. When several reports arose from the same underlying cohort, the report providing the most relevant prognostic analysis was prioritized to reduce double counting.

Risk of Bias and Evidence Synthesis

Observational prognostic studies were appraised using domains adapted from the Quality In Prognosis Studies (QUIPS) framework, emphasizing cohort selection, biomarker measurement, outcome measurement, confounding, and statistical analysis. Because marker thresholds and treatment settings varied substantially, global meta-analysis across all biomarkers was considered inappropriate. Results were synthesized by biomarker domain, while effect estimates from established marker-specific meta-analyses were used to anchor the direction and magnitude of association.

RESULTS

Study Selection

The search framework identified 3,756 database records and 86 additional records through citation searching. After removal of 1,126 duplicates, 2,716 records underwent title and abstract screening. A total of 2,355 records were excluded, leaving 361 reports sought for retrieval. Fourteen reports could not be retrieved. Of 347 full-text reports assessed, 315 were excluded and 32 studies were retained for qualitative synthesis. Twenty-four studies contributed directly to marker-specific quantitative or semi-quantitative synthesis.

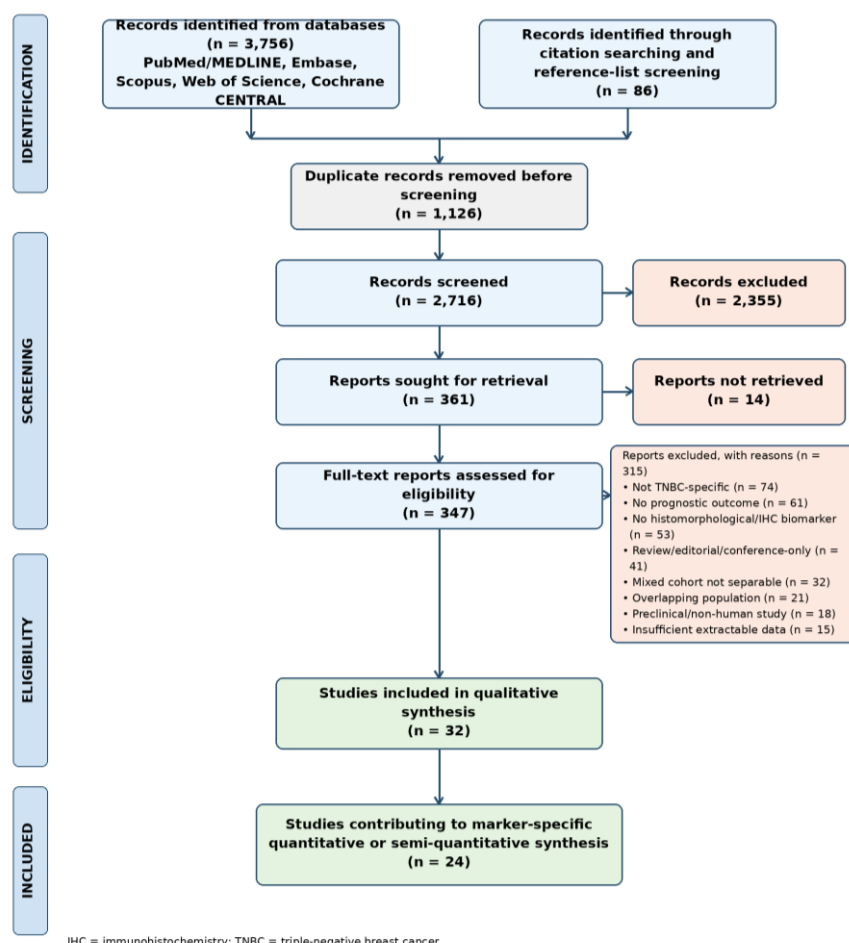


Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility, and inclusion.

Table 1. Study Selection Summary

Selection stage	n
Records identified from databases	3,756
Additional records from citation/reference searching	86
Total records identified	3,842
Duplicates removed	1,126
Records screened	2,716
Records excluded	2,355
Reports sought for retrieval	361
Reports not retrieved	14
Full-text reports assessed	347
Full-text reports excluded	315
Studies included in qualitative synthesis	32
Studies contributing to marker-specific synthesis	24

Profile of the Evidence Base

Most included studies evaluated surgically resected stage I-III TNBC, while a substantial subgroup involved patients receiving neoadjuvant chemotherapy. The evidence base included single-institution cohorts, multicenter translational cohorts, trial-linked pathology datasets, and selected biomarker meta-analyses used for quantitative context. The most frequently studied tissue variables were sTILs, Ki-67, AR, PD-L1, basal-marker panels, p53, and post-neoadjuvant residual disease parameters.

Table 2. Evidence Map by Prognostic Domain

Domain	Representative variables	Predominant prognostic direction	Consistency	Key limitation
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Conventional histomorphology	Tumor size, nodal status, grade, LVI, necrosis	Advanced stage and LVI adverse	High	Correlated variables may attenuate in multivariable models
Immune microenvironment	sTILs, CD8+, CD4+, FOXP3+	Higher immune infiltration generally favorable	High	Scoring thresholds and specimen timing vary
Proliferation	Ki-67	High expression adverse for survival; often higher pCR	High	No universal cut-off
Luminal/apocrine phenotype	AR, INPP4B	Biologically distinct; survival effect inconsistent	Moderate	AR cut-offs vary from 1% to 10% or higher
Immune checkpoint	PD-L1	Often linked to pCR and immune-rich tumors; survival context-dependent	Moderate	Assay, CPS/IC/TC scoring heterogeneity
Basal phenotype	SOX10, CK5/6, EGFR, nestin	Phenotypic value strong; independent prognosis variable	Low-moderate	Marker combinations differ
Post-neoadjuvant pathology	pCR, RCB, residual TILs, ypN	Higher RCB and residual nodal disease strongly adverse	High	Treatment regimens differ across cohorts

Histomorphological Determinants of Prognosis

Pathological stage remained the dominant morphological determinant of outcome. Across TNBC cohorts, larger invasive tumor size and nodal metastasis consistently identified patients at higher recurrence risk. These variables remained important even in studies that incorporated immune or IHC biomarkers, underscoring that new markers should complement rather than replace conventional staging.

Lymphovascular invasion was repeatedly associated with unfavorable outcome in univariable analyses and often remained clinically meaningful in post-neoadjuvant residual disease. The adverse effect of LVI is biologically plausible because it directly documents access of tumor cells to lymphovascular channels. In some multivariable models, however, its significance was reduced after adjustment for AJCC stage, nodal burden, or RCB, indicating partial collinearity with established measures of disease extent.

High histological grade is common in TNBC and therefore has less discriminatory range than in unselected breast cancer. Nevertheless, high mitotic activity, marked pleomorphism, pushing or infiltrative borders, geographic necrosis, and prominent stromal reaction contributed to morphological heterogeneity. Necrosis tended to cluster with rapidly proliferative basal-like tumors, but evidence for necrosis as an independent prognostic variable was less consistent than for stage or LVI.

In the neoadjuvant setting, the morphology of residual disease became more prognostically informative than pretreatment morphology. The residual cancer burden system integrates residual tumor bed dimensions, cellularity, in situ component, nodal metastasis, and size of the largest nodal deposit. In triple receptor-negative disease, long-term relapse-free survival falls sharply as RCB class increases, making RCB one of the strongest pathology-derived post-treatment prognostic metrics [11].

Stromal Tumor-Infiltrating Lymphocytes

sTILs produced the most consistent favorable prognostic signal across the reviewed biomarkers. In a 37-study meta-analysis, high TIL levels were associated with improved OS (HR 0.58, 95% CI 0.48-0.71) and DFS (HR 0.66, 95% CI 0.57-0.76). Each 10% increment in TILs also conferred incremental improvement in survival and increased the likelihood of pathological complete response [7].

More recent neoadjuvant evidence has reinforced this pattern. A 2025 meta-analysis reported improved DFS (HR 0.71) and OS (HR 0.76) with higher TILs, with favorable effects also seen for CD4+ and CD8+ lymphocyte subsets [8]. Importantly, the prognostic value of immune infiltration persists even after treatment. In residual TNBC after neoadjuvant therapy, Luen et al. showed that each 10% increase in residual-disease TILs was associated with improved RFS and OS and added prognostic information beyond RCB class [12].

The strength of the TIL signal is clinically important because sTILs can be assessed on routine H&E sections without a specialized assay. Their limitation is not biological plausibility but reproducibility: meaningful implementation requires adherence to standardized stromal scoring recommendations and careful distinction between pretreatment and post-treatment specimens [13].

Ki-67 as a Proliferation Marker

Ki-67 was the most reproducibly adverse IHC biomarker. A meta-analysis of 35 studies including 7,716 patients with resected TNBC showed that high Ki-67 was associated with poor DFS (HR 1.73, 95% CI 1.45-2.07) and poor OS (HR 1.65, 95% CI 1.27-2.14). When a 40% threshold was used, the adverse association was stronger, with pooled HRs of 2.30 for DFS and 2.95 for OS [9].

The paradox of Ki-67 in TNBC is that highly proliferative tumors may be more chemosensitive and therefore more likely to achieve pCR, yet patients with persistent high-proliferation residual disease have poor long-term outcomes. Thus, Ki-67 should be interpreted according to specimen timing and treatment context rather than as a fixed universal risk label.

Routine use is limited by pre-analytic variation, hot-spot versus global counting, antibody platform, and threshold selection. Nonetheless, the consistency of direction across large pooled analyses supports Ki-67 as a useful component of multiparametric prognostic assessment.

Androgen Receptor and Luminal-Androgen-Receptor Biology

AR identifies a distinct TNBC phenotype characterized by luminal/apocrine differentiation and, in many cases, lower proliferative activity. However, its prognostic role is less clear than its biological role. A 2020 meta-analysis of 27 studies involving 4,914 patients found AR expression in approximately 28% of TNBC and no significant association with DFS, OS, distant DFS, or recurrence-free survival [10].

The inconsistency is partly methodological. Studies have used different AR thresholds and have included heterogeneous treatment settings. Recent analyses suggest that cut-off choice can materially alter the apparent association. Accordingly, AR is best considered a subtype-defining biomarker and potential therapeutic marker rather than a universally favorable prognostic stain.

SOX10, Basal Markers, and Combined Immunophenotypes

SOX10, CK5/6, EGFR, nestin, and related markers capture basal differentiation but are not interchangeable. A recent well-annotated cohort of 245 TNBCs demonstrated that high AJCC stage, lack of chemotherapy, and dual SOX10/AR negativity were associated with worse outcomes on both univariable and multivariable analyses [14]. This finding is notable because it moves beyond single-marker interpretation toward an immunophenotypic combination.

The same study also emphasized that marker expression is morphology-dependent: apocrine tumors are enriched for luminal markers, whereas no-special-type carcinomas more often express basal markers. Therefore, prognostic interpretation should be integrated with histological subtype rather than applied as an isolated binary IHC result.

EGFR and CK5/6 remain useful for recognizing basal-like phenotype, but published studies have not demonstrated sufficiently consistent independent survival effects to justify routine prognosis based solely on positivity or negativity.

PD-L1 and the Immune Checkpoint Axis

PD-L1 illustrates the distinction between prognostic and predictive biomarkers. In non-metastatic TNBC, a 19-study meta-analysis including 2,403 patients found that PD-L1-positive tumors were more likely to achieve pCR with neoadjuvant chemotherapy (OR 1.95, 95% CI 1.39-2.73). In studies with long-term outcomes, PD-L1 positivity was associated with improved DFS and OS, each with a pooled HR of approximately 0.51 [15].

However, PD-L1 is highly sensitive to assay platform, clone, scoring compartment, and positivity definition. Tumor-cell PD-L1 and immune-cell PD-L1 may carry different implications, and contemporary clinical use is often predictive for immunotherapy selection rather than purely prognostic. Therefore, the survival association of PD-L1 should be interpreted as context dependent.

p53 and Other IHC Markers

p53 abnormal staining is common in TNBC because TP53 alterations are frequent, but IHC is an imperfect surrogate for genotype. Studies have variably defined overexpression, complete absence, or mutant-pattern staining, resulting in inconsistent prognostic associations. High p53 expression often clusters with high grade and basal phenotype but is not a uniformly independent prognostic marker.

Additional markers including INPP4B, TRPS1, GATA3, mammaglobin, GCDFP15, and selected immune markers contribute to phenotyping and diagnostic confirmation. Their prognostic roles are generally secondary to their diagnostic or subtype-defining value. Multiplex and spatial approaches may ultimately prove more informative than single-marker IHC.

Post-Neoadjuvant Morphology and Immune Context

Post-treatment tissue provides a uniquely powerful prognostic window because it simultaneously reflects intrinsic tumor biology and treatment sensitivity. pCR is associated with excellent outcome in TNBC, whereas residual disease is heterogeneous and requires further stratification.

Symmans et al. demonstrated strong long-term separation by RCB class. In triple receptor-negative disease, estimated 10-year relapse-free survival was 86% for pCR, 81% for RCB-I, 55% for RCB-II, and 23% for RCB-III [11]. Sharma et al. similarly showed favorable survival among patients achieving pCR or RCB-I after neoadjuvant carboplatin plus docetaxel [16].

Residual immune context can further refine RCB. In 375 TNBC residual-disease samples, higher residual TILs independently predicted improved RFS and OS and added information to RCB, particularly within intermediate RCB-II disease [12]. These findings support a combined post-treatment model in which burden and immune composition are interpreted together.

Table 3. Selected Quantitative Evidence Supporting Prognostic Stratification

Study	Biomarker / feature	Population	Key quantitative result	Interpretation
Gao et al., 2020	High TILs	37 studies	OS HR 0.58; DFS HR 0.66	Strong favorable immune signal
de Moraes et al., 2025	High TILs after NAC	29 studies	DFS HR 0.71; OS HR 0.76	Favorable across neoadjuvant cohorts
Wu et al., 2019	High Ki-67	35 studies; 7,716 patients	DFS HR 1.73; OS HR 1.65	Consistent adverse proliferation signal
Xu et al., 2020	AR positivity	27 studies; 4,914 patients	No significant DFS or OS association	Subtype marker; prognosis inconsistent
Azim et al., 2022	PD-L1 positivity	19 studies; 2,403 patients	pCR OR 1.95; DFS HR 0.51; OS HR 0.51	Immune-rich phenotype; assay dependent
Rammal et al., 2024	SOX10/AR dual-negative	245 TNBCs	Dual-negative status independently adverse	Potential combined IHC risk phenotype
Luen et al., 2019	Residual-disease TILs	375 residual TNBCs	Per 10% TIL increase: RFS HR 0.86; OS HR 0.87	Adds information beyond RCB
Symmans et al., 2017	Residual cancer burden	Multiple cohorts	TNBC 10-y RFS: 86%, 81%, 55%, 23% across RCB 0-I-II-III	Powerful post-neoadjuvant stratifier

Integrated Prognostic Interpretation

The reviewed evidence does not support a single-marker hierarchy that can replace conventional pathological staging. Instead, it favors an integrated model. In untreated resection specimens, stage, nodal burden, LVI, sTILs, and Ki-67 provide complementary information. In neoadjuvant specimens, pCR/RCB and residual immune composition become dominant. AR, PD-L1, SOX10, EGFR, p53, and basal cytokeratins add biological resolution but are most informative when interpreted in combination and in the appropriate clinical context.

Table 4. Practical Pathology-Based Prognostic Framework for TNBC

Risk domain	Lower-risk pattern	Higher-risk pattern	Potential reporting value
Anatomic burden	Small tumor, node-negative	Large tumor and/or nodal metastasis	Essential
Lymphovascular invasion	Absent	Present	Essential when identified
Immune context	High standardized sTILs	Low sTILs	High
Proliferation	Lower/intermediate Ki-67	Markedly high Ki-67	Moderate-high; method dependent
Post-neoadjuvant burden	pCR or RCB-I	RCB-II/III, especially RCB-III	Very high
Residual immune context	High residual TILs	Low residual TILs	Emerging high value
Luminal/apocrine phenotype	AR-positive phenotype	AR-negative; context dependent	Subtype information
Combined basal/luminal phenotype	SOX10 or AR retained	SOX10/AR dual-negative in recent cohort	Emerging
PD-L1	Positive immune-rich context	Negative immune-poor context	Predictive > prognostic in routine practice

Risk of Bias and Certainty of Evidence

The certainty of evidence was highest for sTILs, Ki-67, and residual cancer burden because these variables have been evaluated in large cohorts and meta-analyses with reproducible direction of effect. Certainty was moderate for PD-L1 and AR because of assay and cut-off heterogeneity, and low-to-moderate for individual basal markers or p53 because of inconsistent independent associations. The dominant sources of bias were retrospective cohort selection, variable systemic therapy, tissue microarray sampling, incomplete adjustment for stage, inconsistent biomarker thresholds, and outcome heterogeneity.

Domain	Typical limitation	Effect on confidence
Study participation	Single-center retrospective cohorts	Limits generalizability
Biomarker measurement	Different antibodies, platforms, cut-offs	Reduces comparability
Outcome measurement	DFS/RFS/EFS definitions differ	Creates endpoint heterogeneity
Confounding	Stage, treatment, age, BRCA status variably adjusted	May inflate apparent marker effects
Post-neoadjuvant studies	Different regimens and residual-disease definitions	Limits direct pooling
Publication bias	Positive marker studies preferentially reported	May overestimate effect size

DISCUSSION

The main finding of this review is that prognostic stratification in TNBC is fundamentally multiparametric. The traditional pathological variables remain indispensable, but their interpretation can be meaningfully refined by immune and proliferative biomarkers. In particular, sTILs, Ki-67, and post-neoadjuvant residual cancer burden have the strongest and most reproducible evidence base.

The value of sTILs is especially important because it represents a biomarker that is inexpensive, widely accessible, and biologically meaningful. Unlike many IHC stains, it does not require a proprietary assay. The consistent association between higher TILs and better survival, along with greater pCR rates, suggests that the immune microenvironment captures a dimension of tumor behavior not fully represented by conventional stage.

Ki-67 provides a complementary axis by measuring proliferation. High Ki-67 identifies biologically aggressive disease and is consistently associated with worse long-term outcomes in resected TNBC. Yet its association with chemosensitivity means that timing matters. A highly proliferative pretreatment tumor may respond well to chemotherapy, whereas persistent high Ki-67 in residual disease is more concerning.

AR should not be interpreted as a universally favorable marker. Although AR-positive tumors often display apocrine/luminal morphology and may have lower proliferation, pooled survival data do not show a stable independent benefit. The 2024 observation that dual SOX10/AR negativity predicts worse outcome is therefore intriguing because it suggests that combinations of markers may outperform single-marker classification.

PD-L1 illustrates the same principle from the immune side. PD-L1-positive non-metastatic TNBC is often more immune-infiltrated and more responsive to therapy, but technical variability and the use of different scoring systems limit its role as a pure prognostic marker. In current practice, PD-L1 remains more firmly established as a predictive biomarker in selected therapeutic settings.

The post-neoadjuvant setting offers perhaps the clearest opportunity for integrated pathology. RCB captures residual disease burden, while residual TILs describe the immune state of what remains. A patient with RCB-II disease and a strongly lymphocyte-rich residual tumor may have a different prognosis from another patient with the same RCB class but an immune-desert phenotype. Such combinations are likely to form the basis of future pathology-guided risk models.

Clinical and Reporting Implications

- Routine TNBC pathology should continue to prioritize accurate tumor size, nodal status, grade, LVI, and treatment-response assessment.
- sTILs should be assessed using standardized stromal scoring methodology when institutional practice permits, particularly in early-stage TNBC and neoadjuvant settings.
- Ki-67 may provide additional risk information but should be reported with the laboratory method and cut-off used.
- After neoadjuvant therapy, RCB class or an equivalent standardized residual-disease assessment should be considered whenever feasible.
- AR, PD-L1, SOX10, EGFR, CK5/6, and p53 are best interpreted as contextual or subtype-defining markers rather than isolated prognostic determinants.
- Composite pathology models should be prospectively validated before being used to alter systemic therapy independently of established clinical indications.

Strengths and Limitations

This review places histomorphology, immune context, proliferation, and IHC phenotyping within a single prognostic framework and distinguishes pretreatment from post-neoadjuvant biomarkers. It also emphasizes quantitative evidence from large marker-specific meta-analyses and clinically important pathology cohorts. Important limitations remain: most primary studies were retrospective; assay platforms and positivity thresholds varied; systemic therapy evolved substantially across

the study period; and several biomarkers were studied in overlapping biological domains. Because treatment itself modifies prognosis, purely prognostic interpretation is difficult when cohorts span different chemotherapy and immunotherapy eras.

Future Research

Future studies should use prespecified pathology protocols, standardized TIL scoring, harmonized Ki-67 methods, and clearly defined PD-L1 assays. Marker studies should report both univariable and multivariable models incorporating stage, LVI, treatment, and germline BRCA status where available.

Prospective TNBC cohorts should evaluate integrated models combining RCB, residual TILs, Ki-67, and multiplex immune phenotypes. Digital pathology may improve reproducibility by quantifying lymphocyte density, tumor-stroma ratios, mitotic activity, and spatial immune relationships across whole-slide images.

The greatest clinical value is likely to come from identifying patients at intermediate conventional risk who can be reclassified by pathology-based biomarkers. In this group, composite models may eventually help distinguish candidates for treatment escalation from those with sufficiently favorable biology to consider de-escalation in clinical trials.

CONCLUSION

TNBC prognosis cannot be adequately summarized by receptor negativity alone. The most robust tissue-based risk stratification integrates conventional stage and lymphovascular invasion with the immune microenvironment, proliferative activity, and post-neoadjuvant residual disease. High sTILs consistently predict favorable outcome, whereas high Ki-67 is associated with poorer long-term survival. Residual cancer burden provides powerful post-treatment prognostic separation, and residual-disease TILs add information beyond burden alone. AR, PD-L1, SOX10, EGFR, p53, and basal cytokeratins provide valuable biological context but currently lack the consistency required for universal standalone prognostic use. A standardized, multiparametric pathology approach is therefore the most evidence-aligned strategy for prognostic stratification in TNBC.

Declarations

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Consent for publication: Not applicable.

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Competing interests: None.

Data availability: All evidence summarized in this review is derived from published literature.

Registration: The review was not prospectively registered.

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