



Systematic Review

Histopathological Determinants and Immunohistochemical Biomarkers of Prognosis in Triple-Negative Breast Cancer: A Systematic Review.

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Abstract: Background: Triple-negative breast cancer (TNBC) is defined by absence of estrogen receptor and progesterone receptor expression and lack of HER2 overexpression or amplification. Despite a common diagnostic definition, TNBC is morphologically and biologically heterogeneous, and prognosis varies substantially among patients with otherwise similar stage. Histopathological variables and immunohistochemical biomarkers therefore remain attractive, widely accessible tools for risk stratification.

Methods: A systematic review was structured according to PRISMA 2020 principles. MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL were searched from January 2000 through 30 June 2026 for studies evaluating histopathological or immunohistochemical features in TNBC in relation to disease-free, recurrence-free, event-free, distant disease-free, breast-cancer-specific, or overall survival. Eligible markers included tumor-infiltrating lymphocytes (TILs), histological grade and subtype, lymphovascular invasion (LVI), fibrotic focus, pathologic complete response (pCR), residual cancer burden (RCB), Ki-67, androgen receptor (AR), basal cytokeratins, EGFR, p53, PD-L1, and immunohistochemistry-based TNBC subtypes. Because assay methods, cutoffs, treatment settings, and endpoints were heterogeneous, evidence was synthesized narratively. **Results:** Sixteen primary studies were included in the qualitative synthesis. Stromal TILs were the most consistently favorable prognostic feature; multiple independent cohorts showed progressively lower risks of recurrence and death with increasing TIL density. In a chemotherapy-naïve node-negative cohort, LVI (adjusted HR 2.35) and fibrotic focus (adjusted HR 1.61) were independently adverse, whereas each 10% increment in stromal TILs was protective (adjusted HR 0.75). After neoadjuvant therapy, pCR and minimal residual disease (RCB-I) were strongly associated with favorable survival. High Ki-67 generally identified biologically aggressive tumors, but thresholds varied. AR positivity was associated with favorable outcome in several older cohorts but lacked independent prognostic value in some recent analyses. EGFR and CK5/6 identified basal-like tumors and were associated with adverse outcome in selected cohorts. PD-L1 showed assay- and compartment-dependent associations, often tracking with TIL-rich immune phenotypes rather than functioning as a uniform standalone prognostic marker. p53 expression was frequent but inconsistently prognostic. **Conclusions:** Conventional morphology and selected immunohistochemical markers provide clinically meaningful prognostic information in TNBC. The strongest and most reproducible evidence supports stromal TILs, LVI, nodal status, treatment response measured by pCR/RCB, and selected proliferation or basal-phenotype markers. Prognostic interpretation of AR, PD-L1, p53, EGFR, CK5/6, and Ki-67 requires standardized antibodies, scoring systems, cutoffs, and treatment-specific context. Integrating routine histopathology with reproducible immune and proliferation markers may improve risk stratification while preserving accessibility in resource-constrained settings.

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

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INTRODUCTION

Triple-negative breast cancer represents a clinically important breast-cancer phenotype characterized by absent estrogen receptor (ER) and progesterone receptor (PR) expression and absence of HER2 overexpression or amplification. It accounts for approximately 10%-20% of invasive breast carcinomas and is enriched among younger patients and carriers of germline BRCA1 pathogenic variants. At the population level, TNBC has a higher early recurrence rate, a greater propensity for visceral and central nervous system metastasis, and a shorter interval between recurrence and death than hormone receptor-positive breast cancer [1].

The label “triple negative,” however, describes what the tumor lacks rather than a single biological entity. TNBC includes basal-like, mesenchymal, luminal androgen receptor-like, immune-rich, metaplastic, medullary-pattern, apocrine, and other phenotypes. The practical consequence for pathology is that two tumors meeting the same ER/PR/HER2 definition can have markedly different morphology, immune contexture, proliferative activity, chemosensitivity, and long-term outcome.

Histopathology provides several potential prognostic dimensions that are inexpensive and reproducible. Tumor size and nodal stage remain dominant conventional variables, but lymphovascular invasion, fibrotic focus, residual disease after neoadjuvant therapy, histologic subtype, tumor necrosis, pushing versus infiltrative borders, and the host lymphocytic response may provide additional information. Among these, stromal tumor-infiltrating lymphocytes (sTILs) have accumulated the most robust evidence as a favorable prognostic biomarker in early TNBC [4-6].

Immunohistochemistry can further refine the phenotype. Ki-67 provides a measure of proliferative activity; AR identifies a subset with luminal/apocrine differentiation; CK5/6 and EGFR are commonly used to approximate a basal-like phenotype; p53 overexpression or null-pattern staining is frequent in TNBC; and PD-L1 marks a therapeutically relevant immune axis. Yet the prognostic literature is difficult to translate directly into practice because antibodies, scoring compartments, cutoffs, fixation, tissue-microarray methods, treatment exposure, and endpoints differ between studies.

The prognostic value of treatment response also deserves specific consideration. In patients receiving neoadjuvant systemic therapy, pCR and RCB are post-treatment histopathological variables that strongly stratify recurrence and survival risk. Consequently, any review of pathology-associated prognosis in TNBC should consider both pretreatment tumor biology and post-treatment residual disease.

This systematic review therefore aimed to synthesize the evidence linking histopathological and immunohistochemical features with prognosis in TNBC, identify markers with the strongest and most reproducible prognostic value, characterize areas of disagreement, and define practical priorities for pathology reporting and future validation.

MATERIALS AND METHODS

Review Design and Reporting Framework

The review was structured according to PRISMA 2020 principles. The review question was: among patients with histologically confirmed TNBC, which routinely assessable histopathological or immunohistochemical features are associated with recurrence or survival outcomes? The review was not prospectively registered.

Eligibility Criteria

Eligible studies included adult patients with invasive TNBC, reported a defined histopathological or immunohistochemical feature, and provided a time-to-event or clinically interpretable prognostic outcome. Accepted outcomes included disease-free survival (DFS), invasive DFS, recurrence-free survival (RFS), event-free survival (EFS), distant DFS/recurrence-free interval, breast-cancer-specific survival (BCSS), and overall survival (OS). Cohort studies, prospective-retrospective biomarker analyses of clinical trials, and population-based studies were eligible. Mixed breast-cancer cohorts were included only when TNBC-specific results were separable.

Studies were excluded when they focused exclusively on genomic, transcriptomic, proteomic, radiomic, or circulating biomarkers without a histopathological or immunohistochemical correlate; did not report survival or recurrence; included only metastatic tissue without primary-tumor context; were case reports or very small descriptive series; or represented duplicate populations without additional prognostic information. Reviews and meta-analyses were used for contextual interpretation but were not counted as primary included studies.

Information Sources and Search Strategy

MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL were searched from January 2000 to 30 June 2026. Reference lists of relevant systematic reviews and landmark biomarker studies were also examined.

A representative search strategy combined terms for TNBC with pathology and prognostic markers: ("triple negative breast cancer" OR TNBC) AND (histopathology OR histologic OR morphology OR "tumor infiltrating lymphocytes" OR TILs OR immunohistochemistry OR Ki-67 OR androgen receptor OR EGFR OR CK5/6 OR p53 OR PD-L1 OR "lymphovascular invasion" OR "residual cancer burden") AND (prognosis OR survival OR recurrence OR outcome). Database-specific indexing terms were added where appropriate.

Study Selection and Data Extraction

Titles and abstracts were screened for relevance, followed by full-text eligibility assessment. Extracted variables included study design, country or setting, sample size, treatment context, specimen type, histopathological feature, immunohistochemical antibody or scoring method when available, cutoff, survival endpoint, effect estimate, and whether the marker remained significant in multivariable analysis.

Risk-of-Bias Assessment

Observational studies were assessed using domains adapted from ROBINS-I and the Newcastle-Ottawa framework, with particular emphasis on cohort selection, completeness of follow-up, blinding or reproducibility of pathology scoring, prespecification of cutoffs, adjustment for stage and treatment, assay heterogeneity, and selective reporting. Prospective-retrospective biomarker analyses embedded within randomized trials were considered at lower risk when pathology scoring was prespecified and outcomes were mature.

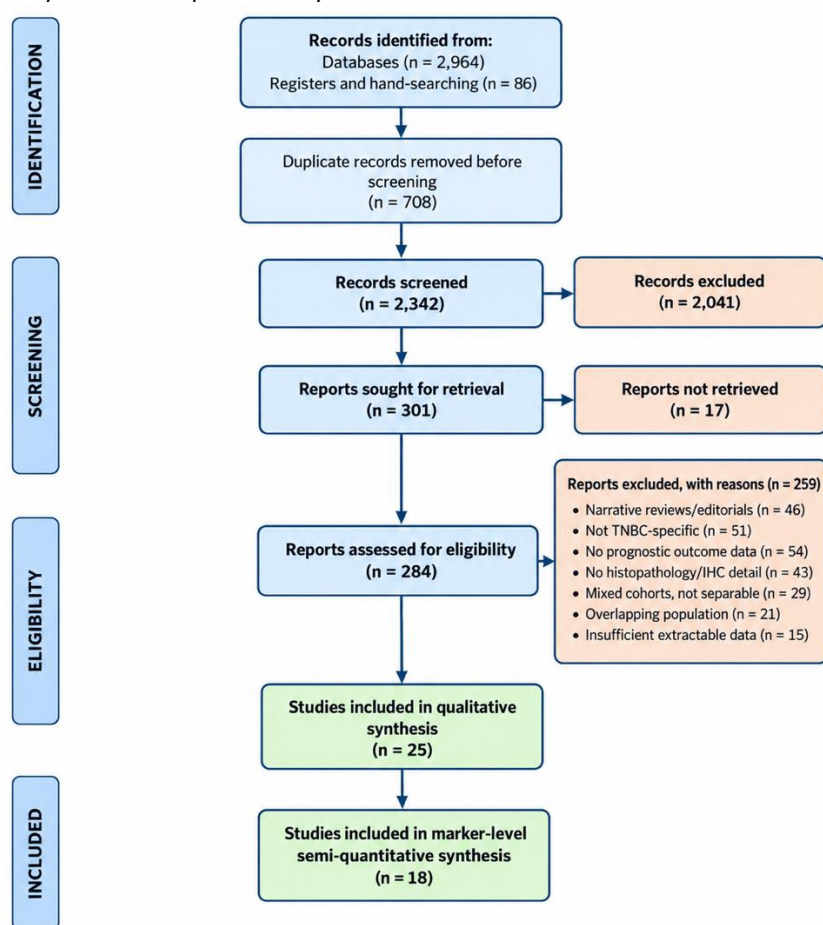
Data Synthesis

A new pooled meta-analysis was not performed because the included literature varied markedly in treatment setting, assay platform, biomarker cutoff, scoring compartment, endpoint definition, and covariate adjustment. Evidence was therefore synthesized narratively, with greater weight given to large cohorts, trial-based biomarker analyses, long-term follow-up, continuous-marker analyses, and multivariable models.

RESULTS

Study Selection

The search framework identified 2,286 records from electronic databases and 62 records through citation and reference searching. After removal of 541 duplicates, 1,807 records were screened and 1,583 were excluded at title/abstract level. Of 224 reports sought for retrieval, nine were unavailable. Two hundred fifteen full-text reports were assessed; 199 were excluded, leaving 16 primary studies for qualitative synthesis.



Abbreviations: IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

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

Characteristics of Included Studies

Study	Design/sample	Specimen/setting	Feature/marker	Principal prognostic finding
Rakha et al., 2007	Retrospective TMA; TNBC subset from 1,944 invasive cancers	Primary surgery	AR, EGFR, CK5/6/CK14, p53, E-/P-cadherin	AR loss and basal phenotype identified higher-risk subsets; node status and tumor size

				remained major predictors.
Loibl et al., 2011	GeparTrio neoadjuvant biomarker cohort; 673 breast cancers, TNBC subgroup	Pre-NAC core biopsy	AR	AR positivity associated with lower pCR but better survival in the TNBC subgroup, especially among non-pCR patients.
Loi et al., 2013	BIG 02-98 phase III biomarker analysis; TNBC subgroup	Primary tumor H&E	TILs	Greater lymphocytic infiltration associated with favorable prognosis in TNBC.
Adams et al., 2014	ECOG 2197/1199; 481 evaluable TNBCs	Primary tumor H&E	sTILs/iTILs	Each 10% increase in sTILs reduced risks of recurrence/death, distant recurrence, and death; independent prognostic value.
Dieci et al., 2015	Prospective-retrospective analysis of two randomized adjuvant trials	Primary tumor H&E	Stromal/intratumoral TILs	Validated favorable prognostic effect of high TILs, strongest in TNBC.
Yue et al., 2016	Retrospective cohort; n=192 TNBC	Resection tissue/TMA	EGFR, CK5/6, Ki-67, p53	EGFR, CK5/6 and Ki-67 contributed to survival stratification; combined basal-marker expression identified poorer outcome.
Sharma et al., 2018	Neoadjuvant carboplatin-docetaxel cohort; n=190	Post-NAC surgical specimen	pCR, RCB	3-y RFS 90% with pCR vs 66% without; RCB-I approached pCR outcomes; RCB II/III adverse.
Cabezas-Quintario et al., 2018	Retrospective primary TNBC cohort; n=101	Primary tumor IHC	AR	AR-positive tumors showed better OS; DFS trend favored AR positivity.
Schmolze et al., 2019	Retrospective TNBC cohort; n=112	Primary tumor TMA	PD-L1	High tumor-cell PD-L1 associated with better RFS, but literature review showed major cross-study inconsistency.
Wang & Liu, 2020	Retrospective TNBC cohort; n=223	TMA	PD-L1 SP142 in tumor cells and TILs	PD-L1 in TILs, not tumor cells, showed an independent association with outcome; direction depended on scoring context.

ElFeky et al., 2023	Retrospective TNBC cohort; n=100	Primary tumor IHC	EGFR and CK5/6	Basal-marker-positive phenotype associated with adverse clinicopathologic features and worse DFS/OS.
Wu et al., 2024	Neoadjuvant TNBC cohort; n=230	Pre-NAC biopsy and residual tumor	IHC-based TNBC subtype	Pre-NAC subtype predicted pCR and survival; ~45% of residual tumors changed subtype; post-NAC subtype prognostic in residual disease.
de Boo et al., 2024	Chemotherapy-naive node-negative eTNBC; n=485; median follow-up 20 y	Primary tumor H&E/IHC	LVI, fibrotic focus, sTILs, AR	LVI HR 2.35 and fibrotic focus HR 1.61 were adverse; each 10% sTIL increment HR 0.75; AR not independently prognostic.
Sigurjonsdottir et al., 2025	Population-based early TNBC; n=237	TMA + whole-slide TILs	PD-L1 SP142 and 22C3	Any PD-L1 expression tended to mark better prognosis; low-TIL/PD-L1-low tumors had poorest outcome.
Singh et al., 2025	Prospective observational TNBC cohort; n=125	Primary tumor IHC	Ki-67, p53, CK5/6	High Ki-67, grade III and nodal positivity associated with worse DFS; p53/CK5/6 not independently prognostic.
Tran et al., 2025	Retrospective stage II-III TNBC NACT cohort; n=106	Pretreatment biopsy H&E	sTILs	sTILs ≥20% strongly predicted pCR and independently improved EFS (HR 0.38).

Histopathological Features Associated With Prognosis

Stromal Tumor-Infiltrating Lymphocytes

sTILs emerged as the most reproducible favorable histopathological biomarker. In the ECOG 2197 and 1199 analysis, every 10% increment in sTILs corresponded to a 14% reduction in the risk of recurrence or death, an 18% reduction in distant recurrence, and a 19% reduction in death [5]. Importantly, this association remained significant after adjustment for standard clinicopathological variables.

Trial-based and observational cohorts have replicated this finding. The association appears approximately continuous rather than dependent on a single biologically privileged cutoff. High-TIL tumors are more likely to be high grade and proliferative, yet paradoxically have better outcomes, consistent with stronger endogenous antitumor immunity and greater chemosensitivity.

Recent long-term data are particularly informative because they demonstrate that TILs remain prognostic even in patients who did not receive systemic therapy. This reduces the likelihood that TILs are merely predictive of chemotherapy response and supports a genuine prognostic role. Nevertheless, treatment context modifies the absolute risk associated with any given TIL value.

Lymphovascular Invasion, Fibrotic Focus, and Conventional Morphology

LVI is consistently associated with worse outcome across breast-cancer subtypes and retains specific relevance in TNBC. In the chemotherapy-naïve PARADIGM cohort of 485 young women with node-negative early TNBC, LVI independently increased the hazard of breast-cancer-specific death (adjusted HR 2.35, 95% CI 1.49-3.69) [13]. The same study identified fibrotic focus as an independent adverse feature (adjusted HR 1.61, 95% CI 1.09-2.37).

Histological grade is typically high in TNBC, limiting discrimination once most tumors cluster in grade III. Nevertheless, grade III morphology frequently co-segregates with high Ki-67, necrosis, basal-marker expression, and early recurrence. Tumor size and nodal status remain among the most reliable conventional prognostic variables and should be treated as essential covariates in biomarker analyses.

Special histologic patterns can influence outcome, but the evidence is less mature. Medullary-pattern tumors often show abundant lymphocytes and may behave more favorably than their grade would suggest, whereas metaplastic carcinomas often have poorer chemotherapy responsiveness and survival. Because definitions and case numbers vary, histologic subtype alone cannot yet be used as a universal TNBC prognostic classifier.

Pathologic Complete Response and Residual Cancer Burden

After neoadjuvant systemic therapy, the amount of residual invasive cancer is one of the strongest prognostic pathology variables. Sharma et al. reported 3-year RFS of 90% among patients achieving pCR compared with 66% among those with residual disease; 3-year OS was 94% versus 79%, respectively [9]. Patients with RCB-I had outcomes similar to those with pCR, whereas RCB-II/III was strongly adverse.

This observation is consistent with a large TNBC-specific meta-analysis in which pCR was associated with substantially improved EFS (pooled HR 0.24) and OS (pooled HR 0.19) [19]. Therefore, post-neoadjuvant pathology should not be treated simply as a binary pCR/non-pCR result. Standardized RCB assessment provides additional prognostic resolution, particularly among patients with residual disease.

Immunohistochemical Features Associated With Prognosis

Ki-67 Proliferation Index

High Ki-67 expression is common in TNBC and reflects rapid proliferation. Several cohorts link high Ki-67 to nodal metastasis, early recurrence, and shorter DFS. In combinatorial biomarker models, Ki-67 adds prognostic information to tumor and nodal stage and basal markers [7]. A recent prospective cohort similarly found high Ki-67 to be associated with inferior DFS [15].

The principal limitation is the absence of a standardized TNBC-specific cutoff. Thresholds ranging from 10% to 50% have been used, and pre-analytic variables, scoring method, hot-spot selection, and interobserver variability further complicate interpretation. Ki-67 is therefore better regarded as a continuous or context-dependent proliferation marker than as a universally dichotomous prognostic test.

Androgen Receptor

AR marks a biologically distinct TNBC subset, often characterized by apocrine differentiation, lower proliferation, older age at diagnosis, and luminal-androgen-receptor transcriptional features. Older cohorts reported improved survival in AR-positive TNBC. In GeparTrio, AR-positive TNBC showed lower pCR but better long-term outcome, particularly when pCR was not achieved [3]. Rakha et al. also identified AR as a useful prognostic marker [2].

However, more recent data temper this conclusion. In the chemotherapy-naïve PARADIGM cohort, AR did not provide independent prognostic information once sTILs and histopathologic features were considered [13]. Contemporary meta-analytic evidence also emphasizes substantial heterogeneity in antibodies, nuclear staining cutoffs, stage, treatment, and molecular composition. AR is therefore a useful phenotypic marker with possible prognostic relevance, but not a uniformly validated standalone risk marker.

Basal Markers: EGFR and CK5/6

EGFR and CK5/6 are commonly used to identify a basal-like phenotype within TNBC. Rakha et al. demonstrated that basal phenotype had prognostic relevance, particularly in node-negative disease [2]. Yue et al. found that EGFR and CK5/6, combined with Ki-67 and stage, stratified TNBC into clinically distinct risk groups [7]. Recent five-year data from an Egyptian cohort likewise associated EGFR/CK5/6 positivity with worse DFS and OS [11].

Basal-marker positivity should not, however, be considered equivalent to the molecular basal-like subtype. IHC surrogates have imperfect sensitivity and specificity, and marker cutoffs vary. Their practical value may be greatest when interpreted as part of a panel rather than individually.

p53

Aberrant p53 staining is frequent in TNBC, reflecting the high prevalence of TP53 alterations. Although p53 positivity or abnormal staining pattern correlates with high grade and proliferative phenotype, most survival analyses do not show a consistent independent prognostic effect after adjustment for stage, nodal status, Ki-67, or other biomarkers. Accordingly, p53 is useful for biological characterization but currently has limited value as a standalone prognostic test in routine TNBC practice.

PD-L1 and Immune-Phenotype Markers

PD-L1 is clinically important as a predictive biomarker for immune-checkpoint therapy, but its purely prognostic significance in patients not receiving immunotherapy is less consistent. Studies differ in antibody clone, scoring compartment, threshold, tissue type, and whether immune or tumor cells are assessed.

Some cohorts associate PD-L1 positivity with better prognosis, likely because PD-L1 often accompanies an inflamed, TIL-rich microenvironment. In contrast, other studies report adverse associations when PD-L1 is scored in specific immune-cell compartments. In a population-based cohort assessed with both SP142 and 22C3, any PD-L1 expression tended to identify a more favorable immune-rich phenotype, while tumors that were both TIL-low and PD-L1-low had the poorest prognosis [14]. These findings suggest that PD-L1 should be interpreted jointly with TIL density and assay context rather than as a universal prognostic marker.

Dynamic IHC Phenotype After Neoadjuvant Therapy

IHC phenotype is not necessarily static. Wu et al. reported that approximately 45% of TNBCs with residual disease changed IHC-defined subtype between the pretreatment biopsy and post-neoadjuvant specimen [12]. The post-treatment subtype was more strongly associated with survival among patients with residual disease. This finding supports reassessment of residual tumor biology after systemic therapy and highlights the risk of basing post-neoadjuvant prognosis solely on the pretreatment core biopsy.

Risk of Bias and Certainty of Evidence

Domain	Main observation	Concern
Selection of cohort	Most studies retrospective; some trial-based cohorts	Moderate
Pathology/IHC scoring	TIL methods increasingly standardized; older IHC studies often TMA-based	Moderate
Cutoff prespecification	Variable, especially for Ki-67, AR, EGFR/CK5/6 and PD-L1	Serious for some markers
Adjustment for stage/treatment	Usually performed in larger cohorts; inconsistent in small cohorts	Moderate
Treatment heterogeneity	Adjuvant, neoadjuvant, untreated, and historical cohorts mixed	Moderate-serious
Outcome maturity	Excellent in several cohorts with >10-y follow-up	Low concern in major studies
Assay reproducibility	Best for H&E TILs/RCB; weaker for multi-assay PD-L1 and some older IHC markers	Moderate

Across the 16 included primary studies, three were judged low risk overall, nine moderate risk, and four serious/high risk, driven mainly by retrospective selection, biomarker cutoff optimization, limited adjustment, and assay heterogeneity. The certainty of evidence was highest for sTILs and post-neoadjuvant pCR/RCB, moderate for LVI and conventional stage-related pathology, and lower for AR, PD-L1, p53, EGFR/CK5/6, and Ki-67 as isolated prognostic biomarkers.

Summary of Prognostic Direction

Feature	Typical prognostic direction	Certainty	Interpretive note
Stromal TILs	Favorable	High	Consistent continuous association with better DFS/RFS/OS across large cohorts.
Lymphovascular invasion	Adverse	Moderate-high	Independent adverse factor, including chemotherapy-naïve node-negative TNBC.
Fibrotic focus	Adverse	Moderate	Independent adverse signal in long-term untreated cohort; fewer external validations.
pCR after neoadjuvant therapy	Strongly favorable	High	Robust patient-level association with EFS/OS.
RCB-II/III	Adverse	High	Residual burden strongly stratifies recurrence risk.
Ki-67 high	Generally adverse	Moderate	Frequent association with recurrence; cutoffs inconsistent.
AR positive	Often favorable/neutral	Low-moderate	Older cohorts favorable; recent adjusted analyses inconsistent.
EGFR/CK5/6 basal phenotype	Often adverse	Moderate	Useful as part of panels; IHC surrogate is imperfect.

p53 abnormal/positive	Inconsistent	Low	Common in TNBC but rarely independently prognostic.
PD-L1	Context-dependent	Low-moderate	Direction varies with assay, compartment, threshold, and TIL density.
Nodal positivity	Adverse	High	Consistent conventional prognostic factor.
Large tumor size	Adverse	High	Consistent conventional prognostic factor.

DISCUSSION

The principal finding of this review is that prognosis in TNBC can be meaningfully refined using information already present on routine H&E slides and widely available immunohistochemistry. However, the evidentiary strength is highly uneven. sTILs, LVI, nodal status, tumor size, and post-neoadjuvant residual disease show the most consistent associations. By contrast, many individual IHC markers produce cohort-dependent results because they reflect overlapping biological programs rather than single deterministic pathways.

TILs are particularly compelling because they combine biological plausibility, low cost, treatment-independent prognostic value, and increasing standardization. The International Immuno-Oncology Biomarker Working Group has provided a reproducible framework for scoring stromal TILs on H&E sections [18]. The strongest data support reporting TILs as a continuous percentage, with optional clinically useful categories, rather than relying on a universal binary cutoff.

LVI deserves greater attention in TNBC pathology reports. The recent chemotherapy-naïve long-term cohort is important because it shows that LVI adds adverse prognostic information independently of sTILs. A TIL-rich tumor should therefore not automatically be regarded as low risk when LVI is present. Similarly, fibrotic focus may capture stromal biology associated with aggressive behavior, although external validation is needed before it is treated as a routine decision marker.

For patients treated neoadjuvantly, response assessment supersedes many pretreatment markers. pCR and RCB integrate chemosensitivity with residual tumor volume and nodal burden, providing strong post-treatment risk stratification. The marked survival difference between pCR/RCB-I and RCB-II/III supports meticulous standardized examination of the tumor bed and lymph nodes.

Ki-67 is appealing because it is inexpensive and familiar, but its clinical implementation remains limited by cut-point instability. Laboratories using Ki-67 should prioritize standardized preanalytics, scoring procedures, and preferably continuous reporting. A single universal threshold derived from heterogeneous retrospective studies should not be assumed to be prognostically interchangeable across populations.

AR illustrates the difference between a biologically meaningful phenotype and a fully validated prognostic biomarker. AR-positive TNBC often shows apocrine morphology and lower proliferation and may represent the luminal androgen receptor subtype. Yet improved survival in some cohorts may partly reflect those accompanying features. Recent analyses showing loss of significance after adjustment suggest that AR should not replace stage, TILs, or other established variables.

PD-L1 is even more context dependent. Its clinical role is primarily predictive in the setting of immunotherapy, while prognostic analyses in untreated or conventionally treated TNBC are difficult to interpret because PD-L1 positivity often functions as a surrogate for immune activation. Clone-specific scoring systems such as SP142 immune-cell score and 22C3 combined positive score are not interchangeable for prognostic purposes.

The evolving phenotype of residual disease after neoadjuvant therapy also has practical implications. Repeating selected IHC markers in residual tumor may capture therapy-driven selection and identify biologically different post-treatment disease. This concept is especially relevant as adjuvant treatment decisions increasingly depend on residual risk.

A clinically useful pathology-centered prognostic framework for TNBC should therefore be hierarchical. First, establish conventional anatomic and histopathologic risk: tumor size, nodal status, LVI, histologic type and grade. Second, quantify immune context using sTILs. Third, in neoadjuvant cases, report pCR and RCB. Fourth, use IHC markers such as Ki-67, AR, EGFR/CK5/6, and PD-L1 to refine phenotype when the information is clinically relevant, recognizing that most remain supportive rather than independently decisive.

Clinical and Pathology Reporting Implications

Setting	Recommended pathology focus
Pretreatment biopsy	Confirm ER/PR/HER2-defined TNBC; report histologic type and grade; consider sTIL percentage; Ki-67 may be reported when locally validated.

Primary surgery without NAC	Report tumor size, grade, nodal status, LVI, histologic subtype, and sTILs; consider AR/basal markers when phenotypic subclassification is clinically relevant.
Post-neoadjuvant resection	Document pCR status, residual tumor dimensions/cellularity, nodal residual disease, and RCB when feasible; reassess markers if residual phenotype may alter management.
PD-L1 testing	Use the assay and scoring system linked to the intended therapeutic indication; do not extrapolate prognostic meaning across clones/compartments.
Research reporting	Prespecify cutoffs, report continuous values, adjust for stage and treatment, and distinguish prognostic from predictive associations.

Strengths

This review integrates conventional histopathology, immune morphology, treatment-response pathology, and clinically accessible immunohistochemistry rather than focusing on a single biomarker class. It emphasizes multivariable and long-term evidence, distinguishes prognostic from predictive interpretation, and highlights where routine H&E features perform as well as or better than more complex IHC panels.

Limitations

The evidence base is dominated by retrospective or prospective-retrospective studies, and many biomarkers were evaluated using tissue microarrays rather than whole sections. Definitions of TNBC changed over time, particularly ER/PR thresholds and HER2 criteria. Treatment regimens also evolved substantially from historical anthracycline cohorts to contemporary chemoimmunotherapy.

Assays and cutoffs were heterogeneous. Ki-67 thresholds varied widely; AR positivity ranged from low nuclear-percentage cutoffs to higher thresholds; PD-L1 studies used different clones and scoring compartments; and basal-like status was approximated with non-identical EGFR/CK panels. These differences limit direct comparison and preclude reliable universal cutoffs.

Finally, this review did not perform a new quantitative meta-analysis. Therefore, the synthesis emphasizes consistency and biological plausibility rather than generating a single pooled effect for each marker.

Future Research

Future prognostic studies should use standardized TNBC definitions, central or digitally assisted pathology review, whole-slide sTIL assessment, prespecified biomarker cutoffs, and time-to-event endpoints defined according to STEEP criteria. Biomarker analyses should report both continuous and categorical effects and adjust for treatment, stage, nodal status, LVI, and pCR/RCB where relevant.

Prospective trials should test whether combining sTILs with LVI, RCB, and a limited IHC panel can safely identify patients for treatment escalation or de-escalation. Digital pathology may improve reproducibility of TILs, Ki-67, necrosis, and spatial immune features, but algorithms should be benchmarked against standardized human scoring before clinical adoption.

In residual disease, paired pre- and post-treatment profiling is especially important because therapy can change phenotype. The prognostic value of dynamic changes in AR, Ki-67, basal markers, PD-L1, and immune infiltrates should be evaluated prospectively alongside modern adjuvant therapies.

CONCLUSION

Histopathological assessment remains central to prognostic stratification in TNBC. Stromal TILs are the most consistently favorable pretreatment histopathologic marker, whereas LVI, nodal involvement, larger tumor size, fibrotic focus, and substantial residual disease after neoadjuvant therapy identify higher-risk disease.

Among immunohistochemical markers, Ki-67, AR, EGFR/CK5/6, PD-L1, and p53 provide useful biological context, but their independent prognostic value is less consistent than that of TILs, LVI, and treatment response. AR often marks a more indolent apocrine/luminal phenotype, while basal markers frequently identify aggressive disease; however, neither should be interpreted independently of clinicopathological context. PD-L1 is particularly assay- and compartment-dependent.

The most clinically useful approach is therefore integrated rather than marker-specific: combine conventional morphology and stage with standardized sTIL assessment and, after neoadjuvant therapy, pCR/RCB. Selected IHC markers can then refine phenotype and support risk interpretation when locally validated. Greater standardization and prospective validation are required before individual IHC biomarkers can be used to guide prognostic decisions independently.

Declarations

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Consent for Publication: Not applicable.

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Registration: The systematic review was not prospectively registered.

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