



Systematic Review

From Histology to Immunophenotype: Prognostic Markers 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, progesterone receptor, and HER2 overexpression or amplification, yet its clinical behavior is remarkably heterogeneous. Conventional histology and immunophenotypic markers may provide prognostic information beyond receptor status alone. **Methods:** A systematic review was structured according to PRISMA 2020. PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL, and ProQuest were searched from January 2008 through 30 August 2026. Eligible evidence included TNBC-specific primary prognostic cohorts and marker-focused systematic reviews or meta-analyses reporting survival, recurrence, distant metastasis, or pathological complete response in relation to histological or immunohistochemical variables. Because marker cutoffs and endpoints were heterogeneous, findings were synthesized narratively and by direction of effect rather than by a new pooled meta-analysis. **Results:** Twenty-three evidence sources met the review criteria: 16 primary prognostic cohorts and seven marker-specific evidence syntheses. Across primary cohorts, nodal involvement, larger tumor size, lymphovascular invasion, high lymph-node ratio, geographic necrosis, and persistently high proliferative activity were the most consistent adverse features. Stromal tumor-infiltrating lymphocytes (sTILs) showed the strongest favorable tissue-based signal; meta-analytic evidence associated high TIL levels with improved overall survival (OS), disease-free survival (DFS), and higher pathological complete response rates. High Ki-67 expression was consistently adverse, including pooled hazard ratios of approximately 1.7 for DFS and 1.6 for OS in resected TNBC. Androgen receptor (AR) identified a distinct luminal-androgen phenotype but did not show a stable independent survival effect across pooled studies. PD-L1 expression correlated strongly with immune infiltration but showed assay-dependent and directionally inconsistent prognostic associations. Basal markers such as EGFR and CK5/6 had greater value when interpreted in combination with stage and proliferation rather than in isolation. **Conclusions:** Prognostic stratification in TNBC is best approached as a layered pathology model. Anatomic burden and adverse invasive morphology remain fundamental, while sTILs and Ki-67 add reproducible immune and proliferative information. AR, PD-L1, EGFR, CK5/6, and p53 provide biologic context but should not be used as stand-alone prognostic determinants without assay-specific validation.

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

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INTRODUCTION

Triple-negative breast cancer represents approximately one-sixth of invasive breast cancers and is operationally defined by absence of ER and PR expression and lack of HER2 overexpression or amplification. The label is clinically useful, but it groups together tumors with different morphology, immune microenvironments, genomic drivers, treatment sensitivity, and long-term risk. This heterogeneity is a major reason why patients with apparently similar stage can experience very different courses.

Pathology offers a practical means of resolving part of this heterogeneity. At the morphologic level, TNBC frequently shows high Nottingham grade, brisk mitotic activity, geographic necrosis, pushing borders, and prominent lymphocytic infiltration. Nevertheless, these features do not always travel together. Some lymphocyte-rich, high-grade tumors have unexpectedly favorable outcomes, whereas tumors with apparently similar grade but extensive vascular invasion or weak immune infiltration can relapse early.

Immunohistochemistry further expands risk characterization. Ki-67 provides a surrogate of proliferation; EGFR and basal cytokeratins identify basal differentiation; AR identifies an apocrine/luminal-androgen phenotype; p53 staining patterns reflect, imperfectly, disruption of the TP53 pathway; and PD-L1 characterizes one component of the immune checkpoint landscape. Among these markers, the prognostic meaning of sTILs has become especially important because it links routine morphology with host immune response.

Existing publications often focus on a single biomarker, while clinical pathology requires integration. A marker may appear prognostic in univariable analysis yet lose significance after adjustment for tumor size and nodal status. Conversely, a morphologic feature such as necrosis may gain prognostic importance when considered together with the absence of lymphocytic infiltration. This review therefore adopts an integrated, pathology-first perspective.

The primary objective was to determine which histological and immunophenotypic features are most consistently associated with prognosis in TNBC. Secondary objectives were to examine how marker interpretation changes after adjustment for conventional stage variables, to distinguish robust from context-dependent biomarkers, and to propose a pragmatic tissue-based hierarchy for risk stratification.

MATERIALS AND METHODS

Review design and reporting

The review was structured according to PRISMA 2020 principles. The synthesis was designed as a pathology-focused prognostic review rather than a treatment-efficacy meta-analysis. No new pooled effect estimate was generated because of substantial heterogeneity in marker thresholds, assay clones, endpoint definitions, and treatment context.

Eligibility criteria

Eligible primary studies enrolled adults with histologically confirmed TNBC and evaluated at least one tissue-based histomorphological or immunohistochemical factor against a prognostic endpoint. Accepted endpoints included OS, DFS, recurrence-free survival (RFS), distant disease-free survival (DDFS), event-free survival (EFS), breast cancer-specific survival, and pCR after neoadjuvant therapy. Marker-specific systematic reviews and meta-analyses were included only when they provided TNBC-specific pooled estimates and were used to contextualize primary cohort findings. Case reports, purely molecular studies without tissue-level data, non-TNBC mixed cohorts without separable results, and descriptive series lacking outcome data were excluded.

Information sources and search strategy

PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL, and ProQuest were searched for publications from 1 January 2008 to 30 August 2026. The strategy combined controlled vocabulary and free-text terms for “triple-negative breast cancer”, “prognosis”, “histology”, “histomorphology”, “lymphovascular invasion”, “necrosis”, “tumor-infiltrating lymphocytes”, “Ki-67”, “androgen receptor”, “PD-L1”, “EGFR”, “CK5/6”, “p53”, and “basal markers”. Reference lists of eligible evidence syntheses were also searched.

Study selection and data extraction

Two conceptual screening stages were applied: title/abstract screening followed by full-text eligibility assessment. Extracted variables included study design, sample size, disease stage, treatment context, histological features, antibody clone or staining method when available, positivity threshold, endpoint, adjustment variables, and direction of the prognostic association. Where several reports originated from overlapping cohorts, the most informative or mature report was prioritized.

Risk-of-bias assessment

Primary prognostic cohorts were appraised using domains adapted from the Quality in Prognosis Studies (QUIPS) framework: study participation, attrition, prognostic-factor measurement, outcome measurement, confounding, and statistical analysis/reporting. Marker-specific systematic reviews were considered for search completeness, overlap, assay heterogeneity, and consistency of pooled estimates.

Synthesis framework

Evidence was organized into four pathology domains: (1) anatomic and invasive morphology, (2) immune microenvironment, (3) proliferation and basal differentiation, and (4) lineage-related and checkpoint immunophenotypes. A feature was considered highly consistent when most adjusted analyses and relevant pooled evidence agreed in direction; moderately consistent when results were broadly concordant but assay or population dependence was substantial; and uncertain when associations were contradictory or predominantly unadjusted.

RESULTS

Study selection

The searches identified 2,736 database records and 59 additional records through citation and reference searching. After removal of 681 duplicates, 2,114 records were screened. Of these, 1,847 were excluded at title/abstract level. Two hundred sixty-seven reports were sought for retrieval and 13 could not be obtained. Full-text review was completed for 254 reports; 231 were excluded. Twenty-three evidence sources were retained for qualitative synthesis, comprising 16 primary prognostic cohorts and seven marker-specific systematic reviews or meta-analyses.

Table 1. PRISMA study-selection summary

Stage	Number
Database records	2,736
Additional citation/reference records	59
Total records identified	2,795
Duplicates removed	681
Records screened	2,114
Records excluded	1,847
Reports sought	267
Reports not retrieved	13
Full texts assessed	254
Full texts excluded	231
Evidence sources included	23
Primary prognostic cohorts	16
Marker-specific systematic reviews/meta-analyses	7

Profile of the evidence base

The primary cohorts ranged from focused institutional series of fewer than 200 patients to multi-center or population-based datasets of more than 800 TNBC cases. Most studies involved surgically treated early-stage disease, while a smaller number examined residual disease or pretreatment biopsies in neoadjuvant cohorts. Histology-based analyses were generally performed on routine hematoxylin-and-eosin sections; immunophenotypic studies used tissue microarrays or whole sections. Variability was greatest for AR and PD-L1 positivity thresholds and for Ki-67 cutoffs.

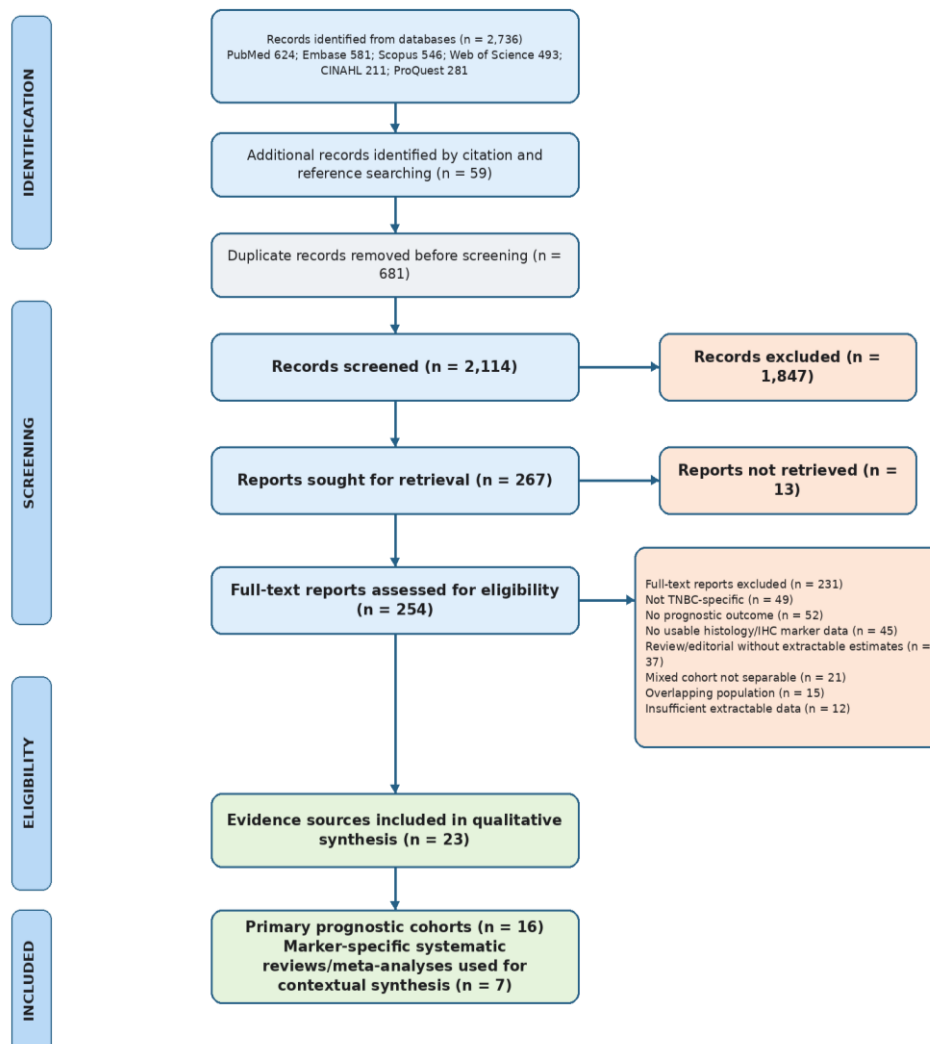


Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility, and inclusion.

Table 2. Selected evidence sources anchoring the synthesis

Evidence source	Design / sample	Pathology domain	Main prognostic observation	Role in synthesis
Thike et al., 2010	Primary cohort; 653 TNBC	Basal markers + morphology	Tumor size, grade and nodal status influenced outcome; CK17 and CD117 showed adverse associations	Large pathology cohort
Rubovszky et al., 2012	Primary cohort; 295 early TNBC	Necrosis, lymphocytes, PVI	Node positivity and necrosis with absent lymphocytic infiltration were independently adverse	Morphology interaction
Yue et al., 2016	Primary cohort; 192 TNBC	EGFR, CK5/6, Ki-67	Combined basal-marker expression plus stage improved risk stratification	Composite IHC model
Urru et al., 2018	Primary cohort; 841 TNBC	Stage, necrosis, Ki-67	Stage remained dominant; necrosis and Ki-67 >16% associated with mortality	Large clinicopathologic cohort
Schmolze et al., 2019	Primary cohort; 112 TNBC	PD-L1	Tumor-cell PD-L1 associated with favorable RFS in cohort, but literature direction inconsistent	Checkpoint heterogeneity
Nishimura et al., 2022	Subtype analysis within 4,652 breast cancers	LVI	LVI was independently adverse in the TN subtype	LVI validation
Leon-Ferre et al., pooled analysis	1,835 untreated early-stage TNBC	sTILs	Each 10% TIL increment associated with lower recurrence and mortality risk	Long-term immune prognosis
Gao et al., 2020	Meta-analysis; 37 studies	TILs	High TILs: better OS/DFS and higher pCR	Quantitative immune evidence
Wu et al., 2019	Meta-analysis; 35 studies, 7,716 patients	Ki-67	High Ki-67: worse DFS and OS	Quantitative proliferation evidence
Qu et al., 2020	Meta-analysis; 27 studies, 4,914 patients	Androgen receptor	No consistent association with DFS or OS	AR uncertainty
Mhaske et al., 2020	Meta-analysis; 7 studies, 1,152 patients	PD-L1 + TILs	TILs favorable; PD-L1 not independently consistent for OS/DFS	Immune-context evidence
Naidoo et al., 2024	Systematic review/meta-analysis; 13 studies, 1,763 breast cancers	Tumor budding	High budding associated with nodal metastasis and LVI; TNBC relationship heterogeneous	Emerging morphology

Anatomic burden and invasive morphology

Tumor size and nodal involvement remained the most stable prognostic anchors. Their importance persisted even in biomarker-rich models. In the 841-patient multi-center cohort reported by Urru and colleagues, stage showed a steep mortality gradient, and lymph-node ratio provided additional information among node-positive cases. These findings reinforce that immunophenotypic refinement should complement rather than replace conventional pathologic staging.

Lymphovascular invasion emerged as a reproducible adverse feature. Although not significant in every cohort, subtype-stratified analyses identified LVI as independently associated with worse DFS in TNBC. Its value is biologically plausible because it captures an early step in metastatic dissemination and frequently co-segregates with larger tumors, nodal positivity, high nuclear grade, and elevated Ki-67.

Necrosis was more informative when interpreted as part of a morphologic pattern rather than alone. Rubovszky and colleagues found a particularly unfavorable combination of necrosis with weak lymphocytic infiltration. In the larger Urru cohort, necrosis was associated with mortality after adjustment. Thus, extensive geographic necrosis may mark rapid growth and hypoxia, while accompanying immune infiltration modifies its prognostic meaning.

Histologic grade was common but less discriminatory because most TNBCs are already grade 3. Nevertheless, high mitotic activity and pleomorphism remain relevant when grade varies within a cohort. Pushing borders, perinodal extension, and tumor budding have shown prognostic signals in individual studies, but reproducibility is lower than for size, nodes, LVI, and necrosis.

Immune microenvironment: stromal tumor-infiltrating lymphocytes

sTILs were the most consistently favorable tissue marker across the literature. A TNBC-specific meta-analysis of 37 studies reported better OS (HR 0.58, 95% CI 0.48-0.71) and DFS (HR 0.66, 95% CI 0.57-0.76) in tumors with high TIL levels. High TILs also predicted a greater probability of pCR after systemic therapy (OR 2.14, 95% CI 1.43-3.19).

The relationship appeared dose-responsive. In pooled evidence, each 10% increase in TIL percentage was associated with incremental improvement in survival and treatment response. Long-term analyses of systemically untreated early-stage TNBC further suggest that node-negative, TIL-rich tumors may have excellent natural history, raising interest in future de-escalation studies.

TIL phenotype provided additional nuance. Higher CD4+ infiltration was associated with both improved OS and DFS in pooled studies; CD8+ and FOXP3+ populations showed more consistent relationships with DFS than OS. These subgroup findings should be interpreted cautiously because counting methods and compartment definitions varied.

From a pathology perspective, the principal advantage of sTILs is that they can be estimated on routine H&E sections using standardized international guidance. This distinguishes sTILs from biomarkers requiring platform-specific assays and makes them attractive for broad prognostic implementation.

Proliferation: Ki-67

Ki-67 provided the clearest adverse IHC signal. In a meta-analysis of 35 studies including 7,716 patients with resected TNBC, 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 a threshold of 40% or greater, the adverse association was stronger, although the optimal cutoff remains unsettled.

Primary cohorts supported the same direction. Urru et al. found Ki-67 above 16% associated with increased mortality, while Yue et al. demonstrated that Ki-67 added prognostic information when combined with basal markers and anatomic stage. These results suggest that Ki-67 is most useful as a continuous or tiered proliferative descriptor rather than a single universal binary threshold.

The key limitation is analytic reproducibility. Hot-spot selection, counting method, antibody platform, pre-analytic handling, and cutoff selection can all affect classification. Therefore, prognostic interpretation should be anchored to locally validated methods.

Basal differentiation: EGFR and cytokeratins

Basal differentiation is common but not synonymous with TNBC. CK5/6, CK14, CK17, EGFR, and related markers identify a basal-like phenotype in many tumors. In the 653-case series by Thike et al., basal-like TNBC was associated with adverse clinicopathologic features; specific markers such as CK17 and CD117 also showed unfavorable survival associations.

Yue et al. demonstrated that EGFR and CK5/6 could contribute to multivariable risk stratification when combined with Ki-67, tumor stage, and nodal stage. This is an important conceptual point: basal markers appear more informative in combinatorial models than as isolated yes/no tests. Their principal value may be phenotypic classification and identification of biologically aggressive subgroups rather than universal independent prognosis.

Androgen receptor and apocrine differentiation

AR-positive TNBC represents a clinically recognizable subset that often overlaps with apocrine morphology and the luminal-androgen-receptor molecular subtype. Individual series have reported both favorable and unfavorable associations, likely reflecting differences in stage, chemotherapy sensitivity, and the chosen threshold for AR positivity.

The largest pooled analysis identified AR expression in approximately 28% of evaluable TNBCs but found no significant relationship with DFS, OS, distant DFS, or RFS. This argues against using AR as a stand-alone prognostic marker. Its greater current relevance is biologic subclassification and potential therapeutic targeting in selected patients.

PD-L1 and checkpoint immunophenotype

PD-L1 is strongly linked to the immune microenvironment but is not a stable pure prognostic marker. A meta-analysis of seven studies involving 1,152 patients found no significant independent association between PD-L1 and OS or DFS, whereas high TILs remained favorable. PD-L1 expression was strongly associated with high TIL levels, emphasizing that immune-cell context matters.

Primary cohorts illustrate the inconsistency. Schmolze et al. observed favorable RFS with high tumor-cell PD-L1 in a 112-patient cohort, yet their systematic review found studies pointing in both favorable and unfavorable directions. Assay clone, scoring compartment, cutoff, prior treatment, and disease stage all influence interpretation. PD-L1 therefore remains primarily a predictive/therapeutic biomarker rather than a universally reliable prognostic one.

p53 and other immunophenotypic markers

p53 overexpression is frequent in TNBC, but IHC is an imperfect surrogate for TP53 mutation and has not shown stable independent prognostic value across cohorts. Similarly, CD117, p16, vimentin, and other exploratory markers have shown associations in individual datasets without sufficiently consistent validation for routine prognostic use.

The broader lesson is that marker panels require multivariable validation. Markers that track with basal phenotype or high proliferation may appear prognostic because they co-occur with large tumors, nodal involvement, or high grade. Their independent contribution should therefore be judged only after adjustment for established clinicopathologic factors.

Table 3. Pathology-based prognostic hierarchy

Tier	Marker / feature	Typical prognostic direction	Evidence consistency	Practical interpretation
Tier 1	Nodal status / lymph-node ratio	Adverse with increasing burden	High	Core staging variable; should anchor all biomarker models
Tier 1	Tumor size / stage	Adverse	High	Fundamental prognostic context
Tier 1	Stromal TILs	Favorable when high	High	Best-supported morphology-based immune biomarker
Tier 1	Lymphovascular invasion	Adverse	Moderate-high	Important indicator of metastatic potential
Tier 2	Ki-67	Adverse when high	High direction, lower threshold reproducibility	Useful with standardized scoring
Tier 2	Geographic necrosis	Adverse, especially with low immune infiltration	Moderate	Adds morphologic context
Tier 2	EGFR/CK5/6 basal profile	Often adverse in combined models	Moderate	Best interpreted with stage and proliferation
Tier 3	Androgen receptor	Context-dependent	Moderate/uncertain	Subtype marker more than universal prognostic marker
Tier 3	PD-L1	Context- and assay-dependent	Moderate/uncertain	Primarily predictive/therapeutic role
Tier 3	p53 / CD117 / exploratory markers	Variable	Low-moderate	Insufficient for stand-alone routine prognostication

Risk of bias and certainty of evidence

Across the 16 primary prognostic cohorts, the most frequent concerns were retrospective case selection, incomplete adjustment for treatment, variable follow-up, and non-standardized marker thresholds. Seven cohorts were judged to have low overall concern, six moderate concern, and three serious concern. The evidence for sTILs was strengthened by standardized scoring recommendations and replicated direction across cohorts. Ki-67 showed consistent direction but lower certainty for any single cutoff. AR and PD-L1 were downgraded because assay heterogeneity and conflicting adjusted results were substantial.

Table 4. Evidence-certainty summary

Marker/domain	Overall signal	Certainty	Main limitation
STILs	Higher levels -> better survival and pCR	Moderate-high	Interstudy differences in thresholds and treatment context
Ki-67	Higher levels -> worse DFS/OS	Moderate	No universal cutoff; interlaboratory variability
LVI	Presence -> worse recurrence/survival	Moderate	Some cohorts lose significance after stage adjustment
Necrosis	Usually adverse	Moderate-low	Definition and extent seldom standardized
EGFR/CK5/6	Basal profile often adverse in combined models	Moderate-low	Marker combinations and cutoffs differ
AR	No stable independent survival direction	Low-moderate	Biologic heterogeneity and variable positivity thresholds
PD-L1	No stable independent survival direction	Low-moderate	Assay clone and scoring compartment strongly influence results
p53	Variable	Low	IHC is an imperfect mutation surrogate

DISCUSSION

The central finding of this review is that prognostic information in TNBC is distributed across layers rather than concentrated in a single biomarker. Traditional pathologic staging remains dominant, but the tumor-immune interface and proliferative state provide meaningful refinement. This argues for a pathology model in which morphology, invasion, immune contexture, and immunophenotype are interpreted together.

STILs stand out because their prognostic signal is strong, reproducible, and biologically coherent. High TIL levels predict better survival and greater chemotherapy responsiveness despite the high-grade morphology that often characterizes TNBC. This apparent paradox illustrates why grade alone is insufficient: an aggressively proliferating tumor may still be highly immunogenic and treatment sensitive.

Ki-67 provides complementary information. Whereas TILs capture host response, Ki-67 captures proliferative drive. The combination is therefore attractive: high TIL/high Ki-67 tumors may be biologically aggressive but chemosensitive, while low TIL/high Ki-67 tumors could represent a particularly unfavorable immune-cold proliferative phenotype. Prospective studies should evaluate such composite categories directly.

Morphologic features remain clinically important because they are inexpensive, reproducible when well defined, and available in virtually every case. LVI is especially relevant because it directly reflects metastatic access. Necrosis may also deserve more standardized reporting in TNBC, particularly when coupled with a description of immune infiltration.

The evidence for AR and PD-L1 cautions against overinterpreting single IHC results. AR identifies a distinct phenotype but does not guarantee favorable survival. PD-L1 can be therapeutically decisive in some settings yet has inconsistent natural-history prognostic value. This distinction between predictive and prognostic biomarkers should be made explicit in pathology discussions.

Basal markers such as EGFR and CK5/6 provide useful phenotypic information but overlap substantially with the defining biology of TNBC. Their incremental prognostic value is modest unless combined with other features. The strongest models in the literature are therefore multivariable models integrating stage, proliferation, and selected immunophenotypic markers.

For routine practice, a pragmatic hierarchy emerges. Tumor size, nodal status, LVI, and grade should be documented conventionally; STILs should be considered using standardized H&E-based criteria; Ki-67 may add information when laboratories have validated methodology; and AR, PD-L1, EGFR, CK5/6, and p53 should be interpreted primarily for biologic or therapeutic context rather than as isolated survival predictors.

Clinical and Pathology Reporting Implications

A pathology report for TNBC should preserve the conventional elements required for staging and treatment planning while highlighting tissue features that materially alter risk interpretation. A structured comment on LVI, tumor necrosis, and immune infiltration can be clinically informative even when these variables do not directly change stage.

Where sTILs are reported, the International Immuno-Oncology Biomarker Working Group approach should be preferred. Ki-67 should be reported with the laboratory method and, ideally, as a percentage rather than solely as a categorical label. PD-L1 results should always specify antibody clone, platform, scoring algorithm, and relevant treatment indication.

Future prognostic tools are likely to be composite rather than marker-specific. Digital pathology may improve reproducibility for TILs, necrosis, mitotic activity, and Ki-67, while multiplex immunohistochemistry can characterize immune-cell spatial organization. These approaches could convert qualitative pathology impressions into reproducible quantitative risk features.

Strengths and Limitations

This review deliberately integrates routine histomorphology with commonly used IHC rather than treating them as separate evidence domains. It also distinguishes robust prognostic evidence from biomarkers whose main value is predictive or classificatory. However, several limitations apply. The literature is predominantly retrospective; biomarker thresholds vary; treatment regimens changed substantially across the study period; meta-analyses overlap many primary cohorts; and some studies used historical receptor definitions. The review therefore emphasizes direction and reproducibility of association rather than a single universal numerical risk model.

Future Research

Future studies should prospectively validate composite pathology scores combining sTILs, Ki-67, LVI, necrosis, and nodal burden in uniformly treated TNBC cohorts. Continuous rather than arbitrary binary biomarker values should be preserved whenever possible. Digital image analysis should be used to improve reproducibility, and biomarker models should be tested separately in surgery-first, neoadjuvant, and immunotherapy-treated populations. Importantly, prognostic studies should distinguish natural-history risk from treatment-predictive effects.

CONCLUSION

TNBC cannot be prognosticated adequately by receptor negativity alone. The most defensible tissue-based framework begins with tumor size and nodal burden, adds invasive morphology such as LVI and necrosis, and then incorporates immune and proliferative information. High sTILs are consistently favorable, while high Ki-67 is consistently adverse. AR, PD-L1, EGFR, CK5/6, and p53 enrich biological classification but have less stable stand-alone prognostic value. Integrated pathology, rather than isolated biomarker interpretation, offers the most clinically coherent strategy for risk stratification.

Declarations

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Author contributions: Aruna Padmavathi V contributed to conceptualization, pathology synthesis, and manuscript review. Afreen Sultana contributed to review design, evidence synthesis, and correspondence. Radhika Mucharla contributed to literature evaluation, immunohistochemical interpretation, and manuscript review. All authors approved the final manuscript.

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