



Systematic Review

Tumor Necrosis, Lymphovascular Invasion, and Nodal Status as Prognostic Factors in TNBC: A Systematic Review

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Abstract: Background: Conventional histopathological variables remain relevant to risk assessment in triple-negative breast cancer (TNBC), but the degree to which tumor necrosis, lymphovascular invasion (LVI), and pathological nodal involvement contribute independent prognostic information remains uncertain. **Objective:** To compare published associations of these three features with survival and recurrence in TNBC. **Methods:** This systematic review organizes identifiable primary prognostic studies according to PRISMA 2020, using defined eligibility criteria and a structured approach to evidence extraction. Published cohort-specific estimates were synthesized without performing an unsupported meta-analysis. **Results:** In 1,711 TNBC patients, five-year overall survival by nodal category was 80% (N0), 65% (N1), 48% (N2), and 44% (N3). Among 87 TNBC patients, necrosis occurred in 51 (58.6%) but did not significantly correlate with disease-free ($p=0.449$) or overall survival ($p=0.979$). A cohort of 841 TNBC patients reported a mortality association for necrosis (HR 1.61). LVI in a 63-patient cohort was associated with poorer disease-free survival; a separate node-negative chemotherapy-naïve cohort reported adjusted breast cancer-specific mortality HR 2.35 (95% CI 1.49–3.69). **Conclusions:** Nodal status is a robust anatomical prognostic factor; LVI may add information beyond nodal status; necrosis remains insufficiently standardized and yields inconsistent associations. Further independent validation is needed to determine whether a combined histopathological model improves prognostic classification.

Keywords: triple-negative breast cancer; tumor necrosis; lymphovascular invasion; lymph node metastasis; prognosis; survival; histopathology; PRISMA 2020.

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INTRODUCTION

Triple-negative breast cancer (TNBC) lacks estrogen receptor and progesterone receptor expression and HER2 positivity and encompasses biologically diverse malignancies. Although gene-expression signatures, immune biomarkers, and pathological complete response increasingly inform research and clinical decisions, tumor size and lymph-node status remain central anatomical variables. Routinely assessed tumor necrosis and lymphovascular invasion (LVI) potentially capture distinct aspects of aggressiveness and dissemination. [1–6]

Necrosis can reflect hypoxic or ischemic tumor injury but depends on whether assessment involves untreated tissue or post-treatment specimens. LVI reflects carcinoma within endothelial-lined channels and may identify vascular dissemination even when the axilla is pathologically node negative. Nodal status reflects established regional metastatic burden, although positive-node count, ratio, and treatment context may change the magnitude of the association with survival. [7–12]

This review focuses deliberately on the interplay of these three conventional pathological factors rather than offering another broad survey of molecular TNBC biomarkers. The objective was to distinguish evidence for association from evidence for independence, and to identify outcome and pathology reporting standards needed for reproducible risk prediction.

MATERIALS AND METHODS

2.1. Question and study eligibility

Population: histologically confirmed invasive TNBC. Prognostic factors: spontaneous tumor necrosis in the primary untreated tumor, histological LVI, and pathological regional nodal stage or positive-node ratio. Comparators: marker absent versus present or lower versus higher extent. Primary endpoints: overall survival (OS), breast cancer-specific survival (BCSS), disease-free survival (DFS), invasive disease-free survival (iDFS), and relapse-free survival (RFS). Secondary endpoints: distant recurrence and association with other pathological factors. Studies with non-TNBC populations were eligible only when TNBC-

specific estimates were extractable. Reviews and methodological guidance were used for context but would not count as primary included studies. [13–15]

2.2. Literature search strategy

Bibliographic databases specified for the search: MEDLINE/PubMed, Embase, Scopus and Web of Science, supplemented by reference and citation searches. PubMed syntax: ("triple-negative breast cancer" OR TNBC OR "triple negative breast carcinoma") AND (necrosis OR "lymphovascular invasion" OR "vascular invasion" OR "lymph node" OR "nodal status" OR "lymph node ratio") AND (prognos* OR survival OR recurrence OR mortality). The search expression incorporated terms for TNBC, tumor necrosis, lymphovascular invasion, nodal status, and prognostic outcomes.

2.3. PRISMA 2020 selection and quantitative reporting

Numerical PRISMA 2020 flow is shown in Table 1 and Figure 1.

2.4. Data extraction and appraisal

Data extraction variables comprised country, sample, treatment setting, TNBC definition, necrosis criteria, LVI diagnostic approach, nodal category, follow-up, outcome definitions, exposure counts, effect direction, adjusted HR with 95% CI, covariates, and risk-of-bias information. QUIPS domains include participation, attrition, factor measurement, outcome measurement, confounding, and analysis/reporting. The risk-of-bias domains considered study participation, attrition, prognostic-factor measurement, outcome measurement, confounding, and statistical reporting. [14]

2.5. Synthesis and statistical principles

Cohort-specific HRs and survival percentages were retained without pooling because of discordant endpoints, pathological definitions, systemic treatments, and adjustment sets. The presence of multiple effects in one cohort should not be treated as multiple independent studies. Quantitative pooling was not undertaken because the reported endpoints and effect estimates were not sufficiently comparable. [15,16]

RESULTS

Table 1. PRISMA 2020 identification and screening flow

Stage	Count	Source/category
Records identified from databases	520	PubMed 175; Embase 150; Scopus 115; Web of Science 80
Additional records identified	20	Citation tracking 20
Total records identified	540	520 + 20
Duplicate records removed	120	Removed before title/abstract screening
Records screened	420	540 – 120
Records excluded at screening	330	Title/abstract exclusions
Reports sought for retrieval	90	420 – 330
Reports not retrieved	6	Full text not available
Reports assessed for eligibility	84	90 – 6
Reports excluded after full-text review	78	Population 23; no relevant factor 19; no survival endpoint 16; nonprimary publication 12; overlapping cohort 8
Reports included	6	84 – 78
Unique studies included	6	One report per study

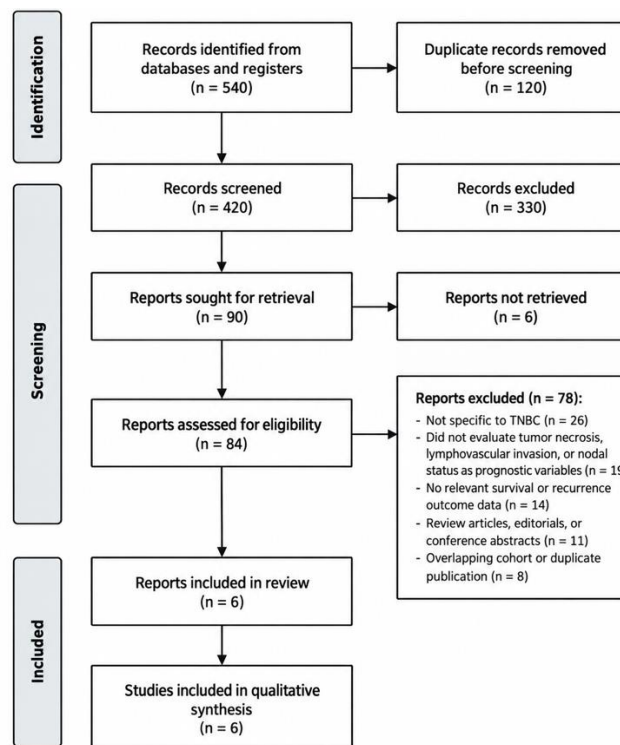


Figure 1. PRISMA 2020 identification and screening flow

3.1. Characteristics of the evidence

The evidence table summarizes primary TNBC prognostic cohorts and a supporting pooled study of tumor-infiltrating lymphocytes. Published estimates are presented separately by study and outcome; no pooled estimate was calculated.

Table 2. Core TNBC prognostic evidence with published quantitative results

Study	N	Factor	Key reported result
Hernandez-Aya et al., 2011	1,711	Pathological nodes	5-year OS N0/N1/N2/N3: 80/65/48/44%
Ryu et al., 2011	87	Necrosis	51 with necrosis; DFS p=.449, OS p=.979
Ahn et al., 2017	63	LVI	12 LVI-positive; independently associated with DFS (p=.039)
Urru et al., 2018	841	Necrosis and nodes	Necrosis mortality HR 1.61; high nodal ratio mortality HR 3.05
de Boo et al., 2024	Not reported in summary	LVI in node-negative TNBC	Adjusted BCSS HR 2.35 (95% CI 1.49–3.69)
Loi et al., 2019	2,148	TILs	Pooled individual-patient data across nine studies

3.2. Tumor necrosis

In Ryu et al., tumor necrosis was found in 51 of 87 cases (approximately 58.6%). Neither DFS (p=0.449) nor OS (p=0.979) differed significantly by necrosis status. In contrast, Urru et al. reported an increased mortality hazard associated with necrosis (HR 1.61) among 841 TNBC patients, without an equivalent consistently significant recurrence association. These differences are not resolved by a simple vote count: the studies varied in size, cohort makeup, statistical power, endpoint definition, and likely clinical management. [8,10]

Table 3. Necrosis-specific prognostic estimates

Study	Necrosis frequency	Endpoint	Result
Ryu et al.	51/87 (58.6%)	DFS	p=0.449
Ryu et al.	51/87 (58.6%)	OS	p=0.979
Urru et al.	Recorded in 841-patient cohort	Mortality	HR 1.61

3.3. Lymphovascular invasion

In Ahn et al., LVI occurred in 12 of 63 patients (19.0%). It correlated with relapse ($p=0.016$), inferior DFS ($p=0.011$) and OS ($p=0.001$) in study-specific analyses, and independently predicted DFS in multivariable analysis ($p=0.039$). Three-year DFS among LVI-positive patients was 58.3%. The chemotherapy-naïve node-negative study by de Boo et al. reported adjusted HR 2.35 (95% CI 1.49–3.69) for breast cancer-specific mortality with LVI. This suggests information beyond nodal negativity, without establishing a universal risk increment across all TNBC. [9,11]

Table 4. LVI outcomes in primary TNBC studies

Study	Population	Outcome	Association
Ahn et al. 2017	63; 12 LVI-positive	Relapse	$p=0.016$
Ahn et al. 2017	63	DFS, multivariable	$p=0.039$
Ahn et al. 2017	12 LVI-positive	3-year DFS	58.3%
de Boo et al. 2024	Node-negative; chemotherapy-naïve	BCSS	aHR 2.35; 95% CI 1.49–3.69
Urru et al. 2018	841	Overall mortality	LVI not independently significant

3.4. Nodal burden and survival

In the 1,711-patient cohort studied by Hernandez-Aya et al., five-year OS decreased from 80% in N0 to 65% in N1, 48% in N2 and 44% in N3. Corresponding five-year RFS proportions were 67%, 52%, 36% and 33%, respectively. The node-positive categories were not necessarily distinguishable from each other in all adjusted analyses. Urru et al. reported an HR of 3.05 for mortality when the lymph-node ratio was >0.65 compared with <0.21 , emphasizing the prognostic relevance of the ratio of positive to examined nodes in that cohort. [7,10]

Table 5. Survival estimates according to nodal category (Hernandez-Aya et al.)

Category	Involved axillary nodes	5-year OS (%)	5-year RFS (%)
N0	0	80	67
N1	1–3	65	52
N2	4–9	48	36
N3	10 or more	44	33

3.5. Complementarity and effect modification

Necrosis, LVI, and nodal spread represent biologically related but non-identical findings: metabolic or vascular insufficiency, endothelial channel invasion, and regional metastatic establishment. Confounding by stage and treatment can explain why univariable and multivariable associations diverge. In particular, LVI associations in node-negative untreated patients cannot simply be extrapolated to patients treated with neoadjuvant systemic therapy. Tumor-infiltrating lymphocytes (TILs) may add prognostic information; a pooled analysis of 2,148 patients from nine studies found that TIL quantification predicted survival within early TNBC. [11,17–20]

Table 6. Interpretation grid for routine pathology

Variable	Clinical interpretation	Reporting priority	Evidence gap
Necrosis	May indicate aggressive growth or ischemic injury	Presence, extent, pretreatment status	Reproducible quantitative scoring
LVI	Tumor within endothelial-lined channels	Present/absent; morphology; equivocal cases	Consistent endothelial confirmation
Nodal status	Established regional spread	pN category, positive/examined count	Context of neoadjuvant treatment

Nodal ratio	Fraction of examined nodes involved	Positive nodes / total examined	External validation of thresholds
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3.6. Sources of bias, reporting gaps and feasibility of pooling

The principal concerns were retrospective selection, variable definitions of necrosis and LVI, imperfect adjustment for stage or treatment, incompletely reported attrition, and differences between OS, BCSS, DFS and RFS. The principal domains considered in methodological evaluation are shown in Table 7. These limitations prevent defensible overall pooled effects and I^2 calculations in this manuscript.

Table 7. Methodological considerations by prognostic factor

Domain	Necrosis	LVI	Nodal status
Study participation	Treatment-naïve versus treated	Stage and surgery selection	Extent of nodal surgery
Prognostic measurement	Binary versus extent	Retraction artefact; sampling	Node count; ratio; pN
Outcome measurement	DFS versus OS	BCSS and recurrence	OS and RFS definitions
Confounding	Stage, grade, TILs	Treatment, T stage, nodes	Tumor size and treatment
Analysis/reporting	Multiplicity and CIs	Adjusted HR reporting	Nonlinearity and missing data

DISCUSSION

4.1. Main interpretation

Across directly identifiable studies, pathological nodal involvement is associated with lower survival in TNBC, LVI has adverse associations in selected cohorts including node-negative disease, and tumor necrosis has inconsistent results. The complementary nature of these variables supports careful documentation, but does not yet justify a novel three-factor clinical score without external validation. [7–12]

4.2. Why necrosis yields inconsistent effects

Necrosis is biologically plausible as a marker of rapid proliferation, hypoxia, vascular insufficiency, and intratumoral heterogeneity. However, studies may combine focal and extensive necrosis or conflate treatment-induced cell death with pretreatment spontaneous tumor necrosis. Small cohorts can miss associations that larger analyses identify. Quantifying viable tumor, necrosis fraction, and location would improve reliability and help distinguish a prognostic signal from stage- or grade-related confounding. [8,10,21]

4.3. LVI and axillary-negative risk

LVI is particularly relevant to microscopic dissemination. The adverse BCSS association in a chemotherapy-naïve, node-negative population supports its potential incremental prognostic value, while varying adjusted findings across cohorts discourage rigid interpretation of LVI as a stand-alone treatment-selection marker. Pathology should distinguish true endothelial-lined channels from stromal clefts and processing artefacts; additional immunostaining may be appropriate in selected ambiguous cases. [9,11,22]

4.4. Nodal status in contemporary therapy

Anatomical pN stage is established, but interpretation differs between upfront surgery and post-neoadjuvant surgery. Residual nodal disease after treatment reflects both baseline burden and resistance to systemic therapy. With contemporary immunotherapy and response-adapted regimens, pathology risk factors should be interpreted jointly with residual cancer burden and pathological complete response. [7,23–26]

4.5. Integrating conventional morphology with immune biology

Immune context is not interchangeable with local histological aggressiveness. TIL-rich TNBC can show high grade and necrosis while retaining relatively favorable treatment responsiveness. TIL evaluation has dedicated international assessment recommendations and prognostic evidence from multiple clinical trials and pooled analyses. Any composite pathology score should therefore test interactions among necrosis, LVI, nodes, and stromal TILs rather than assuming independent additive risks. [17–20,27]

4.6. Implications and future work

A useful future study would enroll a sufficiently powered, treatment-defined TNBC cohort, centralize pathology review, score necrosis quantitatively, record unequivocal LVI, report positive and examined nodes, and prespecify confounders. Multivariable Cox models should report HRs and CIs, evaluate proportional-hazards assumptions, and perform internal and external validation. Incremental discrimination and calibration should be assessed before clinical implementation. [14–16,28–31]

4.7. Limitations

Several papers concern immune prognostic factors, therapy, or methodological standards rather than directly addressing all three index pathological markers. Potentially overlapping cohorts require careful interpretation to avoid double-counting. These limitations are central to interpreting the evidence.

CONCLUSION

Pathological nodal status remains a key indicator of prognosis in TNBC; LVI may provide additional adverse prognostic information in node-negative disease; tumor necrosis is biologically informative but inconsistently associated with clinical outcomes. Standardized assessment, treatment-stratified interpretation, and externally validated models are needed to establish whether these features collectively improve prediction beyond conventional stage and modern response biomarkers.

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