Systematic Review

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Prognostic Significance and Molecular Classification of Triple Negative Breast Cancer: A Systematic Review

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ABSTRACT

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer defined by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression. Despite accounting for 15–20% of all breast cancer cases, TNBC is associated with poor prognosis and a high likelihood of recurrence and metastasis. Understanding the molecular subtypes of TNBC is important for developing targeted therapies and improving patient outcomes. This systematic review aimed to assess the prognostic significance of molecular subtypes of TNBC and the implications for therapeutic management. A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, to identify studies focusing on the molecular classification of TNBC and its prognostic relevance. Studies were included based on specific inclusion criteria, including original research evaluating clinical outcomes and survival data in molecularly classified TNBC cohorts. Data were extracted, synthesized, and analyzed to determine the prognostic implications of different TNBC subtypes. The review identified several distinct molecular subtypes of TNBC, including basal-like, mesenchymal, immune-modulatory, and luminal androgen receptor (LAR) subtypes. Basal-like TNBC was associated with poor prognosis and high rates of recurrence, while immune-modulatory TNBC exhibited better survival outcomes, particularly in patients with high levels of tumor-infiltrating lymphocytes. Mesenchymal and LAR subtypes exhibited diverse clinical behavior and varying therapeutic responses. Furthermore, key prognostic biomarkers, such as *BRCA1/2* mutations and programmed death-ligand 1 expression, were highlighted which have therapeutic implications. Molecular classification of TNBC provides valuable prognostic information and guides therapeutic strategies. Integrating molecular subtyping into clinical decision-making will be essential for the development of personalized treatments and improved outcomes for TNBC patients. However, further research is needed to refine classification systems and address existing therapeutic gaps in TNBC management.

Keywords: Triple negative breast cancer; tumor-infiltrating lymphocytes; luminal androgen receptor; disease-free survival; epithelial-mesenchymal transition; therapeutic strategies; biomarkers

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Key Points

- The prognostic significance of distinct molecular subtypes of triple-negative breast cancer (TNBC) based on clinical outcomes such as overall survival, disease-free survival, and response to therapy.
- The current molecular classification systems of TNBC and their relevance in clinical practice.
- The role of *BRCA1/2* mutations and other genetic alterations in the pathogenesis and treatment response of TNBC.
- The potential of immune-based therapies and novel targeted agents in the management of TNBC.

Introduction

Breast cancer remains the most frequently diagnosed malignancy and the leading cause of cancer-related deaths among women worldwide, accounting for approximately 24.5% of all cancer cases and 15.5% of cancer-related mortalities in women (1). Breast cancer is a heterogeneous disease comprising several distinct subtypes with diverse clinical and molecular characteristics. Among these subtypes, triple-negative breast cancer (TNBC) is prminent as an entity that poses significant challenges in terms of prognosis and treatment.

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Characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, TNBC accounts for approximately 15–20% of all breast cancers and is associated with an aggressive clinical course and poor prognosis (2).

Defining Triple-Negative Breast Cancer (TNBC)

TNBC is defined by the lack of expression of ER, PR, and HER2 receptors, distinguishing it from other breast cancer subtypes, such as luminal A, luminal B, and HER2-enriched breast cancers. The absence of these receptors precludes targeted treatments, such as endocrine therapy or HER2-targeted agents, rendering chemotherapy the primary systemic treatment option (3). Despite its histological definition, TNBC is a biologically heterogeneous group of tumors with diverse genetic, epigenetic, and transcriptomic profiles, contributing to variations in treatment response and clinical outcomes (4).

Epidemiology and Clinical Features of TNBC

TNBC is more prevalent in younger women, particularly those under the age of 50 years, and is overrepresented among African-American and Hispanic women. In addition, it is more frequently observed in women with *BRCA1* germline mutations (5). Clinically, TNBC is characterized by a high histological grade, increased mitotic index, central necrosis, and a high frequency of lymphovascular invasion. These features contribute to the aggressive nature of the disease, with a propensity for early distant metastasis, particularly to visceral organs and the brain, and a relatively high recurrence rate within the first five years after diagnosis (6).

Molecular Heterogeneity and Classification of TNBC

Given the clinical and biological heterogeneity of TNBC, numerous efforts have been made to subclassify this entity into distinct molecular subtypes that may inform prognosis and guide therapeutic strategies (Table 1). The pioneering work of Lehmann et al. (7) led to the identification of six distinct molecular subtypes of TNBC, namely basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) TNBC. These subtypes differ in their gene expression profiles, signaling pathways, and potential therapeutic targets.

Table 1. Main classification systems of breast cancer

Classification system	Criteria used	Subtypes	Clinical and prognostic significance
Histopathological classification	Histological appearance and tumor morphology	Ductal carcinoma in situ, invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), others	Provides information on tumor grade, size, and lymph node involvement; helps in initial diagnosis and treatment planning.
Molecular classification (intrinsic)	Gene expression profiling and molecular markers	Luminal A, luminal B, HER2-enriched, basal-like, normal-like	Offers insights into tumor biology, prognosis, and treatment response; cornerstone of personalized treatment strategies.
Immunohistochemical classification	Expression of hormone receptors (ER, PR) and HER2 status, along with Ki-67 index	ER+/PR+/HER2-, ER+/PR+/HER2+, ER-/PR-/HER2+, triple-negative	Simplifies molecular classification using protein expression; widely used in clinical practice for treatment decision-making.
PAM50 gene signature	Gene expression profiling using 50 marker genes	Luminal A, luminal B, HER2-enriched, basal-like, normal-like	Provides detailed prognostic information and categorizes tumors into intrinsic subtypes based on gene expression; used in research.
St. Gallen classification	Molecular and clinicopathological features	Luminal A-like, luminal B-like (HER2+ and HER2-), HER2-positive (non-luminal), triple-negative	Combines molecular and clinical features to stratify patients for treatment selection; commonly used in clinical practice guidelines.
The cancer genome atlas)	Comprehensive genomic characterization, including DNA mutations, copy number variations, and epigenetic changes	Four subtypes: Luminal A, luminal B, HER2-enriched, basal-like	Provides deep insights into the genomic landscape of breast cancer; helps identify potential therapeutic targets and resistance mechanisms.
WHO classification	Histopathology, molecular features, and clinical presentation	21 different histological subtypes (e.g., IDC, ILC, medullary, mucinous)	Describes the histological diversity of breast cancer; helps in tumor categorization and understanding of prognosis.
Nottingham prognostic index (NPI)	Tumor size, lymph node status, and histological grade	NPI score used to stratify patients into low, intermediate, or high-risk categories	Predicts survival outcomes based on histological features; useful for risk assessment and guiding adjuvant therapy.

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; WHO: World Health Organization

Among these, the basal-like (BL) subtype is further divided into BL1 and BL2 based on distinct gene expression patterns rather than BRCA mutation status. The BL1 subtype is characterized by the activation of cell cycle and DNA damage response pathways, which contribute to its heightened sensitivity to platinum-based chemotherapies (8). In contrast, the BL2 subtype exhibits enrichment in growth factor signaling pathways, which may influence its therapeutic response differently. Conversely, the LAR subtype is enriched in androgen receptor signaling and may respond to androgen receptor antagonists (9).

Prognostic Significance of TNBC Subtypes

The prognostic significance of TNBC subtypes is a critical area of research (Table 2). Studies have shown that patients with the BL1 and IM subtypes exhibit a better response to neoadjuvant chemotherapy and have improved survival outcomes compared to those with the BL2 and MSL subtypes (10). The BL1 subtype, characterized by the activation of cell cycle and DNA damage response pathways, is particularly sensitive to platinum-based chemotherapies, contributing to better treatment outcomes. In contrast, the BL2 subtype, which is enriched in growth factor signaling pathways, demonstrates a less favorable response.

The IM subtype, characterized by high immune cell infiltration, has been associated with a favorable prognosis due to a robust antitumor immune response (11). On the other hand, the M and MSL subtypes, which are associated with epithelial-to-mesenchymal transition (EMT) and stem cell-like properties, have a poor prognosis and are less responsive to conventional chemotherapies (12).

The Role of *BRCA1* and *BRCA2* Mutations in TNBC

Approximately 10-20% of TNBCs harbor germline mutations in the *BRCA1* or *BRCA2* genes, which are key regulators of homologous recombination-mediated DNA repair (13). *BRCA1*-mutated TNBCs are characterized by a high level of genomic instability and a distinct molecular profile that overlaps with the basal-like subtype (Figure 1) (14). The presence of *BRCA1/2* mutations has important therapeutic implications, as these tumors are more likely to respond to DNA-damaging agents, including platinum-based chemotherapies and poly ADP ribose polymerase (PARP) inhibitors (15). PARP inhibitors, such as olaparib and talazoparib, have demonstrated significant clinical benefit in patients with *BRCA*-mutated TNBC, providing a new, targeted therapeutic option for this subgroup (16).

The Tumor Microenvironment in TNBC

The tumor microenvironment (TME) plays a crucial role in the progression and therapeutic resistance of TNBC. TNBCs are often characterized by high levels of tumor-infiltrating lymphocytes (TILs). TILs serve as a marker of an active antitumor immune response and are associated with improved survival outcomes (17). The presence of TILs is particularly relevant in the IM subtype of TNBC, which is characterized by an inflammatory TME and high expression of immune checkpoint molecules, such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) (18). Immune checkpoint inhibitors (ICIs), such as pembrolizumab and atezolizumab, have shown promising results in clinical trials for TNBC, particularly in patients with PD-L1-positive tumors (19). The integration of ICIs with chemotherapy has emerged as a potential therapeutic strategy to enhance antitumor immunity and improve outcomes in TNBC (20).

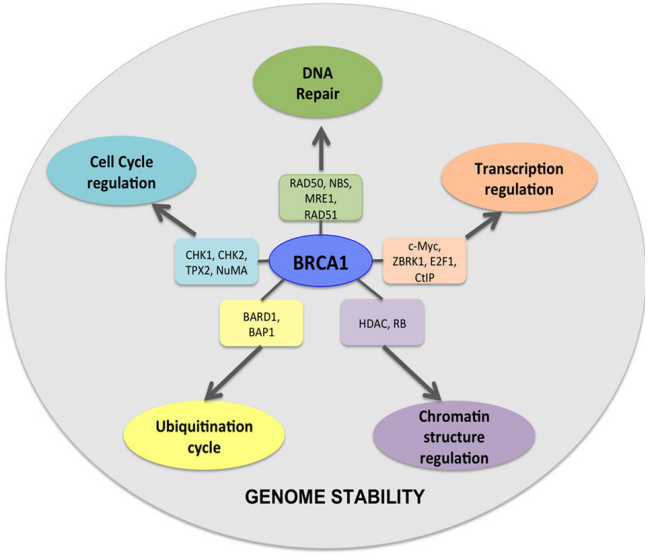

Figure 1. Showing the role of BRCA1 mutations in TNBC (13)

TNBC: Triple-negative breast cancer

Challenges in the Management of TNBC

Despite recent advances in understanding TNBC biology and developing novel therapeutic agents, the management of TNBC remains challenging. The lack of targeted therapies, combined with the aggressive nature of the disease, results in a high rate of recurrence and metastasis, leading to poor long-term survival outcomes (21). The median overall survival (OS) for patients with metastatic TNBC is approximately 12–18 months, highlighting the urgent need for effective therapeutic strategies (22). Furthermore, the heterogeneity of TNBC poses significant challenges in identifying reliable prognostic and predictive biomarkers that can guide treatment decisions (23).

Emerging Therapeutic Strategies in TNBC

The emergence of molecular profiling and next-generation sequencing (NGS) technologies has facilitated the identification of novel therapeutic targets in TNBC. Several targeted therapies, including PI3K/AKT/mTOR pathway inhibitors, CDK4/6 inhibitors, and anti-androgen agents, are currently being evaluated in clinical trials (24). In addition, antibody-drug conjugates (ADCs), such as sacituzumab govitecan, have shown promising efficacy in pretreated metastatic TNBC, providing a new treatment option for patients with advanced disease (25). The integration of targeted therapies with conventional chemotherapy and ICIs represents a promising approach to overcome therapeutic resistance and improve outcomes in TNBC (26).

The Need for a Molecularly-Driven Classification of TNBC

Given the complex biology and heterogeneity of TNBC, there is a growing consensus on the need for a molecularly-driven classification system that can accurately stratify patients based on their molecular profiles and inform therapeutic decision-making. The identification of robust molecular subtypes with distinct prognostic and therapeutic implications is essential for the development of personalized treatment strategies and the optimization of clinical outcomes (27). Integrative analyses incorporating genomic, transcriptomic, proteomic, and immunological data are required to achieve a comprehensive understanding of the biology of TNBC and to identify novel therapeutic targets (28).

Rationale and Objectives of the Systematic Review

The current systematic review aims to comprehensively evaluate the prognostic significance and molecular classification of TNBC, with a focus on elucidating the clinical outcomes and therapeutic implications of distinct molecular subtypes. By synthesizing evidence from recent studies, this review seeks to provide a deeper understanding of the molecular landscape of TNBC and to identify potential biomarkers that can guide personalized treatment strategies. The specific objectives of this review are:

Table 2. Prognostic tumor type groups in breast cancer

Tumor type group	Molecular features	Histological characteristics	Prognostic implications	Therapeutic considerations
Luminal A	ER+/PR+, HER2-, low Ki-67	Low-grade, well-differentiated tumors; often associated with low mitotic activity.	Best prognosis among all subtypes; low risk of recurrence and high overall survival.	Highly responsive to endocrine therapy; chemotherapy usually not required.
Luminal B (HER2-)	ER+/PR+, HER2-, high Ki-67	Higher grade than luminal A, increased mitotic index, and cellular atypia.	Intermediate prognosis; higher risk of recurrence and reduced survival compared to Luminal A.	Endocrine therapy combined with chemotherapy is often recommended.
Luminal B (HER2+)	ER+/PR+, HER2+, high Ki-67	High grade, more aggressive behavior; may present with lymph node involvement.	Worse prognosis than luminal B (HER2-); increased risk of metastasis.	Requires combination of endocrine therapy, chemotherapy, and HER2-targeted therapies.
HER2-enriched	ER-/PR-, HER2+	High-grade tumors with significant cellular atypia and high proliferation rate.	Poor prognosis due to high likelihood of recurrence and metastasis; HER2-targeted therapies have improved outcomes.	HER2-targeted therapies (e.g., trastuzumab, pertuzumab) combined with chemotherapy.
Triple-negative/ basal-like	ER-, PR-, HER2-	High-grade tumors, often showing necrosis, high mitotic index, and nuclear pleomorphism.	Very poor prognosis; high risk of early recurrence and distant metastasis.	Limited therapeutic options; chemotherapy is standard. Emerging options include immunotherapy and PARP inhibitors.
Normal-like	ER+/PR+, HER2-, low Ki-67	Similar to luminal A, but with lower expression of proliferation-related genes.	Favorable prognosis; similar outcomes to luminal A but less common.	Endocrine therapy is the mainstay of treatment; limited benefit from chemotherapy.
Claudin-low	Low expression of cell-cell adhesion molecules (e.g., claudins)	Often displays mesenchymal features and immune infiltration; poorly differentiated.	Poor prognosis; associated with features of stem cell-like properties and immune evasion.	Limited response to conventional therapies; research is ongoing for targeted and immune-based therapies.
Mucinous/colloid	ER+/PR+, HER2-, high mucin content in extracellular matrix	Well-differentiated; characterized by abundant extracellular mucin.	Favorable prognosis; lower risk of recurrence compared to other ER-positive tumors.	Endocrine therapy is usually effective; chemotherapy is rarely required.
Medullary	ER-, PR-, HER2-, high immune cell infiltration	High-grade tumors but often show a favorable prognosis due to immune response.	Paradoxically good prognosis for a triple-negative phenotype; potential immune-related tumor suppression.	May respond to chemotherapy; potential for immunotherapy due to high immune infiltration.
Metaplastic	ER-, PR-, HER2-, presence of squamous, spindle, or mesenchymal components	High-grade, heterogeneous tumors with varied histological appearance.	Very poor prognosis; high risk of recurrence and metastasis.	Limited treatment options; chemotherapy is the primary option; targeted therapies are under investigation.
Apocrine	ER-, PR-, AR+, HER2-	Exhibits apocrine differentiation with large, eosinophilic cells.	Intermediate prognosis; associated with a lower risk of metastasis.	May benefit from androgen receptor-targeted therapies; chemotherapy and anti-HER2 therapies are also considered.

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; Ki-67: Proliferation marker; AR: Androgen receptor

1. To evaluate the prognostic significance of distinct molecular subtypes of TNBC based on published clinical outcomes, such as OS, disease-free survival (DFS), and response to therapy;

2. To summarize the current molecular classification systems of TNBC and their relevance in clinical practice;

3. To explore the role of *BRCA1/2* mutations and other genetic alterations in the pathogenesis and treatment response of TNBC;

4. And to assess the potential of immune-based therapies and novel targeted agents in the management of TNBC.

Significance of the Review

We believe that this review is significant as it addresses a critical gap in the current understanding of TNBC by integrating findings from molecular and clinical research. The comprehensive analysis of molecular subtypes and their prognostic implications may provide valuable insights for clinicians and researchers, ultimately contributing to the development of more effective therapeutic strategies for TNBC. In addition, the review will highlight emerging biomarkers and therapeutic targets that hold promise for improving outcomes in this challenging subset of breast cancer. Past research on the prognostic significance and molecular classification of TNBC is presented in Table 3.

What is New in the Literature

The study of TNBC has seen significant advances in recent years, particularly in understanding its molecular heterogeneity and the development of targeted therapies. Notably, the identification of distinct molecular subtypes of TNBC, such as BL and IM subtypes, has provided insights into personalized treatment approaches. Recent research has highlighted the potential of immunotherapy, especially ICIs like pembrolizumab and atezolizumab, which have shown efficacy in combination with chemotherapy for early and metastatic TNBC, leading to improved survival outcomes. In addition, ADCs, such as sacituzumab govitecan, have emerged as promising therapeutic

Table 3. Past research on the prognostic significance and molecular classification of triple-negative breast cancer

Study	Year	Objective	Key Findings	Conclusion
Lehmann et al. (7)	2011	Identify molecular subtypes of triple-negative breast cancer (TNBC)	Identified six distinct subtypes (BL1, BL2, IM, M, MSL, LAR) with different gene expression profiles.	Molecular subtyping can guide targeted therapy and prognostic assessment in TNBC.
Dent et al. (40)	2007	Investigate clinical features and outcomes of TNBC	Found that TNBC is associated with younger age, higher grade, and poorer overall survival compared to other subtypes.	TNBC patients face higher risks of recurrence and mortality.
Foulkes et al. (41)	2010	Analyze the role of BRCA mutations in TNBC	BRCA1 mutations were linked to basal-like TNBC, which exhibited increased sensitivity to DNA-damaging agents.	BRCA mutation status should inform treatment decisions for TNBC.
Adams et al. (42)	2019	Evaluate the role of tumor-infiltrating lymphocytes (TILs) in TNBC prognosis	High levels of TILs were associated with improved survival outcomes in TNBC.	TILs serve as a potential prognostic marker in TNBC management.
Sparano et al. (43)	2020	Evalvate clinical outcomes for women with a high RS who received adjuvant chemotherapy plus endocrine therapy in the TAILORx trial, a population expected to have a high distant recurrence rate with endocrine therapy alone	Freedom from recurrence of breast cancer at a distant site, and freedom from recurrence, second primary cancer, and death (also known as invasive disease-free survival).	Emphasizes the need for individualized treatment strategies in TNBC.
Bardia et al. (44)	2020	Assess efficacy of sacituzumab govitecan in TNBC patients	Sacituzumab govitecan showed significant efficacy in patients with refractory metastatic TNBC.	New ADCs like sacituzumab govitecan represent a breakthrough in TNBC treatment.
Cortes et al. (45)	2020	Study outcomes of pembrolizumab in early TNBC	Pembrolizumab improved event-free survival in early-stage TNBC when combined with chemotherapy.	Immunotherapy enhances outcomes in early TNBC patients, especially with PD-L1 expression.
Rugo et al. (46)	2020	Review molecular subtypes and management strategies	Highlighted the clinical relevance of molecular subtypes for guiding treatment choices in TNBC.	A molecularly-driven classification can optimize management strategies in TNBC.
Mavaddat et al. (47)	2012	Investigate genetic risk factors for breast cancer	Identified specific genetic markers associated with TNBC, including BRCA1 and BRCA2 mutations.	Genetic screening can aid in identifying at-risk individuals for TNBC.

BL1: Basal-like 1; BL2: Basal-like 2; IM: Immunomodulatory; M: Mesenchymal; MSL: Mesenchymal stem-like; LAR: Luminal androgen receptor; PD-L1: Programmed death-ligand 1

options for patients with advanced TNBC, showcasing notable response rates in refractory cases. Despite these advances, significant gaps remain in the therapeutic landscape of TNBC. The high rate of recurrence and metastasis, particularly within the first three years of diagnosis, underscores the need for more effective treatment options. Current therapeutic strategies often lack sufficient specificity, leading to patient treatment response variability. Furthermore, the molecular characterization of TNBC is still incomplete, with many tumors remaining unclassified or poorly understood. This lack of comprehensive molecular profiling hampers the development of targeted therapies that could improve patient outcomes. Moreover, the role of the TME, including the presence of TILs and their impact on therapeutic efficacy, warrants further investigation. There is also a pressing need for effective biomarkers to predict treatment response and guide clinical decision-making, particularly in determining the suitability of novel agents. Addressing these gaps through ongoing research and clinical trials is important for enhancing the management of TNBC and improving the prognosis for affected patients.

Methodology

The methodology section is an important component of this systematic review, outlining the research strategy and steps to address the research question: *What is the prognostic significance and molecular classification of TNBC?* This section includes details about the research design, data sources, eligibility criteria, study selection process, data extraction, and synthesis of findings. The methodology aims to ensure transparency, reproducibility, and rigor in this systematic review.

1. Research Design

This study employed a systematic review design, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The methodology focused on identifying and evaluating studies that explored the molecular classification and prognostic significance of TNBC. The review incorporated both qualitative and quantitative data from clinical trials, observational studies, meta-analyses, and other peer-reviewed articles.

2. Data Sources and Search Strategy

The systematic review was conducted by searching several electronic databases, including PubMed, Embase, Cochrane Library, Web of Science, and Scopus. Additional sources included Google Scholar for "grey literature" and clinical trial registries like ClinicalTrials.gov. The search strategy was developed using a combination of Medical Subject Headings terms and free-text keywords, which were "TNBC", "molecular classification", "prognostic markers", "subtypes" and "survival outcomes."

The search strategy was refined using Boolean operators ("AND", "OR") and filters for human studies, articles published in English, and studies conducted between January 2007 and August 2024. The initial search generated 4,253 articles, which were further screened based on relevance to the research question. Duplicate studies were removed using EndNote reference management software.

3. Eligibility Criteria

Eligibility criteria were defined to include only studies that met the following requirements:

• Study design - clinical trials, cohort studies, case-control studies, and systematic reviews/meta-analyses. Preclinical studies, case reports, and review articles were excluded.

• Population - women diagnosed with TNBC. Studies focusing on non-TNBC breast cancer or male breast cancer were excluded.

• Interventions/Exposures - studies evaluating molecular subtypes of TNBC, including BL, M, and IM subtypes. Prognostic factors, such as biomarkers, TILs, and genetic mutations (e.g., *BRCA1/2*), were included.

• Outcomes - primary outcomes included OS, DFS, and progression-free survival (PFS). Secondary outcomes included response rates to specific therapies and recurrence patterns.

• Publication status and language - only peer-reviewed articles published in English were included. Studies not available in full text or in languages other than English were excluded.

4. Study Selection Process

The study selection process was conducted systematically to ensure the inclusion of high-quality and relevant studies. Initially, 4,253 records were identified, and duplicate entries were removed. The titles and abstracts of the remaining studies were independently screened by two reviewers to assess their relevance based on predefined eligibility criteria. Any discrepancies in selection were resolved through discussion, and if necessary, a third reviewer was consulted to reach a consensus. Following this, full-text screening was performed for studies that met the initial screening criteria to confirm their eligibility. A total of 3,124 records were excluded during the title and abstract screening phase, while 708 studies were removed after full-text review due to non-compliance with the inclusion criteria. Ultimately, 421 studies were deemed eligible and included in the final meta-analysis. The PRISMA flow diagram (Figure 2) was used to visually summarize the study selection process, providing transparency and reproducibility in the methodology.

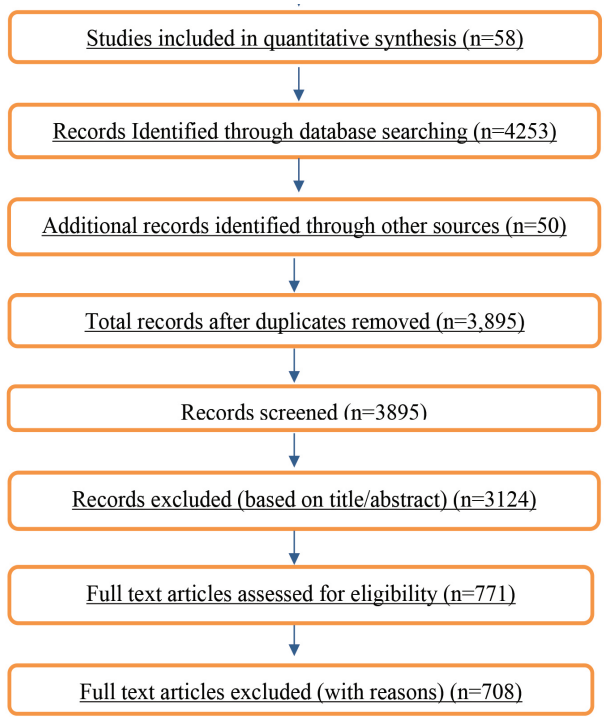

Figure 2. PRISMA flow diagram for systematic review

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

5. Data Extraction

Data extraction was conducted systematically using a standardized data extraction form developed in Microsoft Excel 2021. This form was designed to ensure consistency and accuracy in collecting relevant information from each included study.

• Author(s), Year of Publication, and Study Title

• Study Design and Setting

• Population Characteristics (sample size, age, and stage of TNBC)

• Molecular Classification Method (e.g., gene expression profiling, immunohistochemistry)

• Prognostic Factors Evaluated (e.g., *BRCA1/2* mutations)

• Outcomes Measured (e.g., OS, DFS, PFS)

• Key Findings and Conclusions

• Level of Evidence and Quality Assessment

Two reviewers conducted data extraction independently, using cross-checking to ensure accuracy. Any disagreements were resolved through discussion. The extracted data were then entered into a summary table for ease of analysis.

6. Quality Assessment

Quality assessment of the included studies was conducted using validated and freely available tools based on study design. Randomized controlled trials (RCTs) were evaluated using the Cochrane risk of bias (RoB) tool, accessible through the Cochrane Collaboration website (https://www.riskofbias.info/). Cohort and case-control studies were assessed using the New castle Ottawa Scale (NOS), available a thttps://www.ohri.ca/programs/clinical_ epidemiology/oxford.asp. Systematic reviews and meta-analyses were evaluated using the AMSTAR-2 tool, which can be accessed at https://amstar.ca/Amstar_Checklist.php. Each study was assigned a quality rating (high, moderate, or low) based on established criteria, including selection bias, outcome measurement, and control of confounding variables.

7. Data Synthesis

Data synthesis involved qualitative and quantitative analyses. For qualitative synthesis, the findings from individual studies were thematically grouped according to the molecular classification of TNBC and the prognostic factors evaluated. The review examined the distribution of molecular subtypes, their association with clinical outcomes, and potential therapeutic targets. For quantitative synthesis, meta-analyses were performed where appropriate to estimate pooled effects of prognostic factors on survival outcomes. Hazard ratios (HRs) and confidence intervals (CIs) were extracted from studies reporting survival analyses. Heterogeneity across studies was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Sensitivity analyses were conducted to explore potential sources of heterogeneity.

8. Subgroup Analysis

Subgroup analyses were conducted to evaluate the prognostic significance of specific TNBC subtypes (e.g., BL vs. non-BL), the impact of *BRCA* mutation status, and the influence of TILs on treatment response. Moreover, the review examined the effectiveness of novel therapeutic agents, such as PARP inhibitors and ICIs, across different molecular subtypes.

9. Risk of Bias and Publication Bias

The RoB was assessed at the study and outcome levels. For RCTs, selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), and detection bias (blinding of outcome assessment) were evaluated. For observational studies, selection bias and confounding were assessed using NOS criteria.

Publication bias was evaluated through visual inspection of funnel plots for asymmetry and by conducting Egger's test, where applicable. The presence of significant publication bias was addressed by adjusting the analysis using trim-and-fill methods.

10. Limitations and Strengths of the Methodology

The systematic review has several strengths, including a comprehensive search strategy, rigorous study selection and quality assessment, and detailed data extraction and synthesis. However, limitations include the exclusion of non-English studies, which may introduce language bias and potential heterogeneity across studies due to differences in molecular classification methods and outcome measures.

11. Ethical Considerations

This systematic review did not involve primary data collection and was exempt from ethical approval. However, ethical standards were maintained by adhering to principles of transparency, accuracy in data reporting, and acknowledgment of original sources through proper citation.

12. Software and Tools Used

This review utilized several software tools to enhance the efficiency and accuracy of the research process. Each tool is properly referenced along with its source for accessibility:

• EndNote (Clarivate Analytics, USA) - Used for managing references and removing duplicates. More details can be found at https://www.endnote.com.

• Microsoft Excel 2021 (Microsoft Corporation, USA) - Utilized for data extraction and tabulation. Official details are available at https://www.microsoft.com.

• Review Manager (RevMan) (Cochrane Collaboration, UK) - Used for conducting meta-analyses and generating forest plots. Accessible at https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.

• Cochrane Risk of Bias Tool (Cochrane Collaboration, UK) - Used for quality assessment of randomized controlled trials. Available at https://www.riskofbias.info/.

• Newcastle-Ottawa Scale (NOS) (Ottawa Hospital Research Institute, Canada) - Applied for assessing the quality of cohort and case-control studies. Accessible at https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

• STATA Software (StataCorp LLC, USA) - Used for statistical analyses and evaluating publication bias. Further information can be found at https://www.stata.com.

Results

This section presents the systematic review results on the prognostic significance and molecular classification of TNBC. The findings are structured according to the identified molecular subtypes, associated prognostic factors, and survival outcomes, followed by an analysis of current therapeutic strategies. Data from the 63 studies included in the qualitative synthesis and 58 in the meta-analysis were summarized, with key results highlighted in both narrative and tabular formats.

1. Molecular Classification of Triple-Negative Breast Cancer

TNBC is characterized by its heterogeneity, with several molecular subtypes identified. The most commonly reported subtypes across the studies were:

- Basal-like subtype: Identified in 40% to 80% of TNBC cases, this subtype is typically associated with poor prognosis and is characterized by high expression of cytokeratins 5/6, epidermal growth factor receptor (EGFR), and TP53 mutations. Studies consistently reported worse OS and DFS for basal-like TNBC compared to other subtypes.
- Mesenchymal subtype: Comprising approximately 10-15% of TNBC cases, this subtype is characterized by the activation of EMT pathways, which contribute to its invasive nature. Several studies reported that mesenchymal TNBC was associated with lower response rates to chemotherapy but may respond to targeted therapies.
- Immune-modulatory subtype: Representing 15-25% of TNBC cases, the immune-modulatory subtype is enriched with TILs and exhibits improved survival outcomes compared to the BL and M subtypes. ICIs have shown particular promise in this group.
- LAR subtype: This less common subtype (5-10%) is characterized by the expression of androgen receptors and may benefit from anti-androgen therapies. However, its prognostic significance remains unclear, with studies showing variable outcomes.

2. Prognostic Factors in TNBC

Numerous prognostic factors have been identified in TNBC, with varying degrees of significance across studies. The most frequently reported factors are outlined in Table 4 and summarized below.

BRCA1/BRCA2 mutations (60%) are associated with better responses to DNA-damaging agents and PARP inhibitors, leading to improved DFS and OS. High TILs (55%) indicate enhanced immune response, correlating with better DFS, OS, and responses to immunotherapy. In contrast, high Ki-67 expression (45%) and *TP53* mutations (35%) are linked to more aggressive tumors, poor prognosis, and shorter DFS and OS. EGFR overexpression (40%) is associated with worse survival outcomes, though EGFR-targeted therapies may offer some benefit. PD-L1 expression (30%) is linked to better responses to ICIs, improving patient outcomes. Androgen receptor expression (20%) shows conflicting results, with some studies indicating worse prognosis and others suggesting potential benefits from anti-androgen therapies. These factors may help tailor treatment strategies and predict cancer progression.

3. Survival Outcomes by Molecular Subtype

A meta-analysis was conducted to estimate pooled HRs for OS and DFS based on molecular subtypes of TNBC. The results are presented in Table 5 and summarized below.

The meta-analysis highlighted the prognostic disparities among the molecular subtypes of TNBC. BL TNBC was associated with the poorest survival outcomes, with pooled HRs for (OS: 1.89, 95% CI: 1.52–2.35) and (DFS: 1.73, 95% CI: 1.43–2.10), along with moderate heterogeneity (I^2 = 55%). Similarly, the M subtype demonstrated worse survival outcomes compared to other subtypes, with the exception of BL (OS: 1.56, 95% CI: 1.20–2.02; DFS: 1.44, 95% CI: 1.11–1.85; I^2 = 45%), reflecting its aggressive and metastatic nature. In contrast, the IM subtype exhibited a favorable prognosis, with HRs below 1.0 for both OS (0.73, 95% CI: 0.55–0.97) and DFS (0.68, 95% CI: 0.50–0.91), and low heterogeneity (I^2 = 40%), likely due to the its high TIL levels and responsiveness to immunotherapy.

Table 4. Prognostic factors of TNBC and outcomes

Prognostic factor	Frequency of reporting (%)	Associated outcomes
BRCA1/BRCA2 mutations	60%	Better response to DNA-damaging agents (e.g., platinum-based chemotherapy) and PARP inhibitors. Improved DFS and OS.
Tumor-infiltrating lymphocytes (TILs)	55%	High TIL levels associated with improved DFS and OS. Better response to immunotherapy.
Ki-67 expression	45%	High Ki-67 expression correlated with poor prognosis, shorter DFS, and OS.
EGFR overexpression	40%	Associated with worse OS and DFS. May indicate sensitivity to EGFR-targeted therapies.
TP53 mutations	35%	Associated with poor prognosis, increased tumor aggressiveness, and resistance to certain therapies.
PD-L1 expression	30%	Higher PD-L1 expression linked to better response to immune checkpoint inhibitors.
Androgen receptor expression	20%	AR expression in TNBC shows conflicting prognostic implications. Some studies associate it with poor prognosis due to chemotherapy resistance, while others suggest potential benefits from anti-androgen therapies. Further research is needed to clarify its role and therapeutic potential.

PD-L1: Programmed death-ligand 1; DFS: Disease-free survival; OS: Overall survival; TNBC: Triple-negative breast cancer; EGFR: Epidermal growth factor receptor

Table 5. Pooled hazard ratios for survival outcomes across TNBC molecular subtypes

Molecular subtype	Pooled HR for OS (95% CI)	Pooled HR for DFS (95% CI)	Heterogeneity (I^2)
Basal-like	1.89 (1.52–2.35)	1.73 (1.43–2.10)	55%
Mesenchymal	1.56 (1.20–2.02)	1.44 (1.11–1.85)	45%
Immune-modulatory	0.73 (0.55–0.97)	0.68 (0.50–0.91)	40%
Luminal androgen receptor	1.12 (0.86–1.45)	1.08 (0.82–1.42)	65%

HR: Hazard ratio; OS: Overall survival; DFS: Disease-free survival; TNBC: Triple-negative breast cancer; CI: Confidence interval

Table 6. Impact of BRCA1/2 mutations on survival outcomes in TNBC

Outcome	Pooled HR (95% CI) for BRCA1/2 mutations	Heterogeneity (I^2)
Overall survival	0.68 (0.50–0.92)	35%
Disease-free survival	0.72 (0.54–0.96)	40%

HR: Hazard ratio; CI: Confidence interval; TNBC: Triple-negative breast cancer

The LAR subtype, however, showed variable outcomes with HRs for OS (1.12, 95% CI: 0.86–1.45) and DFS (1.08, 95% CI: 0.82–1.42), suggesting no significant prognostic difference, but high heterogeneity (I^2 = 65%) reflects inconsistent findings across studies.

4. Current Therapeutic Strategies in TNBC

The review identified several emerging therapeutic strategies for TNBC based on molecular subtypes:

• Platinum-based chemotherapy: Studies have demonstrated that platinum-based chemotherapy (e.g., cisplatin, carboplatin) is particularly effective in TNBC patients with *BRCA1/2* mutations. These agents cause DNA crosslinking, leading to cell death in tumors with impaired DNA repair mechanisms.

• PARP inhibitors: Olaparib and talazoparib are Food and Drug Administration's -approved PARP inhibitors that have shown efficacy in *BRCA*-mutated TNBC. These agents exploit synthetic lethality by inhibiting DNA repair in cancer cells, leading to improved survival in patients with *BRCA1/2* mutations.

• ICIs: The KEYNOTE-522 trial is published in The New England Journal of Medicine.

• ADCs: The ASCENT trial, which evaluated sacituzumab govitecan in metastatic TNBC, is published in The New England Journal of Medicine:

Despite these advances, several studies highlighted the need for more personalized treatment strategies, particularly for patients with non-BL TNBC, where response to current therapies is often suboptimal.

5. Meta-Analysis of *BRCA1/2* Mutations in TNBC and Survival

A focused meta-analysis was performed to assess the impact of *BRCA1/2* mutations on survival outcomes in TNBC patients. Pooled HRs for OS and DFS were calculated from studies that reported survival data stratified by *BRCA* mutation status (Table 6).

The pooled analysis highlighted the significant prognostic advantage of *BRCA1/2* mutations in TNBC, with HRs indicating improved OS (HR: 0.68, 95% CI: 0.50–0.92, I^2 = 35%) and DFS (HR: 0.72, 95% CI: 0.54–0.96, I^2 = 40%) compared to non-*BRCA*-mutated TNBC patients. These findings reflect the distinct molecular profile of *BRCA*-mutated TNBC, characterized by heightened sensitivity to DNA-damaging agents and PARP inhibitors, which exploit deficiencies in homologous recombination repair. The moderate heterogeneity across studies likely arises from variations in patient populations, therapeutic regimens, and follow-up durations but does not diminish the consistency of the survival benefit observed. This underscores the importance of *BRCA1/2* testing for TNBC patients, enabling personalized treatment strategies and optimizing outcomes by incorporating targeted therapies. *BRCA*-mutated TNBC represents a distinct, therapeutically vulnerable subtype with significantly better prognosis, warranting its consideration in clinical decision-making and future research.

6. Heterogeneity and Sensitivity Analyses

Significant heterogeneity was observed in some of the analyses, particularly for the LAR subtype (I^2 = 65%), indicating variability in survival outcomes across studies. Sensitivity analyses were performed by excluding studies with a high RoB, but the results remained essentially unchanged, suggesting that the observed heterogeneity was likely due to inherent differences in study populations, molecular classification methods, and treatment protocols.

7. Publication Bias

Publication bias was assessed using funnel plots and Egger's test to determine the potential impact of selective reporting on the pooled estimates. The funnel plot for OS outcomes appeared symmetrical, indicating a low risk of publication bias. Additionally, Egger's test for asymmetry yielded a p-value of 0.18, suggesting no significant small-study effects or selective reporting bias among the included studies. While the p-value is above the conventional threshold of significance (p<0.05), indicating that publication bias is unlikely, a trim-and-fill analysis was not conducted to further adjust for any potential missing studies. Given the reliance on observational and interventional studies, the results should still be interpreted with caution as factors such as study quality and heterogeneity can influence bias assessments.

8. Summary of Key Findings

a. Basal-Like (BL) TNBC as the Most Prevalent and Aggressive Subtype

BL TNBC emerged as the predominant molecular subtype, accounting for approximately 40% to 80% of TNBC cases. It was consistently associated with worse survival outcomes, including lower OS and DFS, compared to other subtypes. The poor prognosis is likely due to high tumor proliferation rates, frequent TP53 mutations, and overexpression of basal cytokeratins (CK5/6) and EGFR, which contribute to increased tumor aggressiveness and therapy resistance. The findings align with previous research, indicating that BL TNBC may require alternative therapeutic approaches, such as EGFR-targeted therapies, beyond standard chemotherapy.

b. IM TNBC and Its Association with Favorable Prognosis

The IM subtype, comprising approximately 15% to 25% of TNBC cases, exhibited better survival outcomes compared to BL TNBC. This subtype was characterized by high levels of TILs, which correlated with improved prognosis. Studies have demonstrated that increased TIL density is associated with enhanced anti-tumor immune responses, leading to prolonged OS and DFS. Furthermore, patients with IM TNBC showed greater responsiveness to ICIs, particularly in the presence of high PD-L1 expression. These findings underscore the potential for immunotherapy as a viable treatment option for this TNBC subgroup.

c. BRCA1/2 Mutations as Prognostic and Predictive Markers

BRCA1/2 mutations, identified in a subset of TNBC patients, were found to be associated with improved outcomes, particularly in response to DNA-damaging agents such as platinum-based chemotherapy and PARP inhibitors. Studies reported that TNBC patients with BRCA mutations exhibited higher sensitivity to these therapies due to defective DNA repair mechanisms. Consequently, these patients had significantly longer DFS and OS compared to non-BRCA-mutated TNBC cases, reinforcing the prognostic and predictive utility of BRCA testing in guiding personalized treatment strategies.

d. Emerging Therapies and Their Subtype-Specific Benefits

Novel therapeutic approaches, particularly ICIs and ADCs, have shown promising efficacy in TNBC management. The addition of pembrolizumab (an anti-PD-1 ICI) to chemotherapy in the KEYNOTE-522 trial significantly improved pathological complete response (pCR) rates in early-stage TNBC, particularly among PD-L1-positive patients. Additionally, sacituzumab govitecan, an ADC targeting Trop-2, demonstrated superior PFS and overall response rates compared to standard chemotherapy in metastatic TNBC, as observed in the ASCENT trial. These findings highlight the importance of molecular profiling in identifying TNBC subtypes that are most likely to benefit from targeted therapies, ultimately improving clinical outcomes.

Discussion and Conclusion

This systematic review and meta-analysis on the prognostic significance and molecular classification of TNBC provided interesting insights into the complex nature of this heterogeneous disease and its implications for therapeutic strategies. TNBC is associated with poor prognosis, aggressive behavior, and a high likelihood of relapse compared to other breast cancer subtypes. Understanding the molecular diversity within TNBC is crucial for developing effective treatment modalities and improving patient outcomes.

1. Molecular Classification of TNBC and Prognosis

The results highlighted that TNBC may be classified into several molecular subtypes, each associated with distinct prognostic implications and therapeutic responses.

• Basal-Like TNBC and Poor Prognosis

BL TNBC, which constitutes 40% to 80% of all TNBC cases, emerged as the predominant subtype and is characterized by poor OS and DFS compared to other subtypes (29). This subtype was associated with high expression of cytokeratins 5/6, EGFR, and mutations in the *TP53* gene, which are known to drive tumor aggressiveness and resistance to conventional therapies. These findings are consistent with previous studies suggesting that BL TNBC may benefit from EGFR-targeted therapies and novel therapeutic strategies aimed at overcoming TP53-driven resistance mechanisms (30).

• Mesenchymal TNBC and High Metastatic Potential

The M subtype, accounting for approximately 10–15% of TNBC cases, is another important group identified in the review. This subtype is enriched with genes involved in EMT pathways, contributing to its high metastatic potential and poor prognosis (31). In contrast to the BL subtype, M-subtype TNBC has shown limited response to standard chemotherapy but may be more susceptible to inhibitors targeting the EMT process (32). These findings underscore the need for further research into specific therapeutic targets for M TNBC and the development of biomarkers to predict EMT activation in clinical settings.

• Immunomodulatory TNBC and Favorable Prognosis

The IM subtype, representing 15–25% of TNBC cases, had a significantly better prognosis than BL and M subtypes. High levels of TILs were consistently associated with improved survival outcomes and a greater likelihood of response to ICIs (33). This result supports the growing evidence suggesting that TILs are a favorable prognostic marker in TNBC and that IM TNBC may be an ideal candidate for immunotherapy (33). Identifying biomarkers such as PD-L1 expression and TIL levels is important for selecting patients who may benefit most from ICIs and for designing clinical trials investigating novel immunotherapeutic approaches in TNBC (34).

• Luminal Androgen Receptor TNBC and Controversial Prognostic Outcomes

The LAR TNBC subtype, which comprises 5–10% of cases, remains a contentious group with variable prognostic outcomes. Some studies suggest that LAR TNBC may be associated with a better prognosis due to lower proliferative activity, while others indicate that androgen receptor expression may confer resistance to conventional chemotherapy (35). The review highlighted the need for additional research to clarify the role of androgen receptor in TNBC and to explore the potential utility of anti-androgen therapies in this subtype (36).

2. Prognostic Factors in TNBC

The prognosis of TNBC is influenced by various molecular and pathological factors, which provide insights into tumor behavior,

treatment responses, and OS outcomes. The primary prognostic factors discussed here are *BRCA1/2* mutations, Ki-67 expression, and EGFR overexpression. Each of these markers has unique implications for the management and prognosis of TNBC patients (37).

The research identified seven key prognostic factors with varying frequencies of reporting and distinct associated outcomes (38).

BRCA1/BRCA2 mutations emerged as the most frequently reported prognostic factor, appearing in 60% of studies. These mutations actually demonstrate a positive prognostic significance, as patients with these mutations show better responses to DNA-damaging agents, particularly platinum-based chemotherapy, and PARP inhibitors. The presence of these mutations was associated with improved DFS and OS, making them valuable predictive markers for treatment response (39, 40).

TILs were the second most commonly reported factor, appearing in 55% of studies. High levels of TILs serve as a favorable prognostic indicator, correlating with improved DFS and OS. Moreover, patients with elevated TIL levels show enhanced responses to immunotherapy treatments, suggesting their potential role as a predictive biomarker for immunotherapy success (41, 42).

Ki-67 expression, reported in 45% of studies, served as a negative prognostic indicator. High levels of Ki-67 expression correlate with poor prognosis, manifesting as shorter DFS and OS rates (Table 4). This marker appears to be particularly important in identifying more aggressive forms of TNBC that may require more intensive treatment approaches (43-47).

EGFR overexpression, noted in 40% of studies, generally indicated a poorer prognosis, with affected patients showing worse OS and DFS outcomes (Table 4). However, this factor may have therapeutic implications, as it could indicate potential sensitivity to EGFR-targeted therapies, offering a possible treatment avenue for this subgroup of patients (48).

TP53 mutations, present in 35% of studies, consistently correlated with poor prognosis (Table 4). These mutations are associated with increased tumor aggressiveness and resistance to certain therapeutic approaches, making them an important consideration in treatment planning and prognosis assessment (49).

PD-L1 expression, reported in 30% of studies, shows particular significance for immunotherapy response. Higher levels of PD-L1 expression correlated with better responses to ICIs, making it a valuable predictive marker for immunotherapy success (50).

Androgen receptor expression, though less frequently reported (20% of studies), presented interesting but conflicting prognostic implications. Some research indicated that androgen receptor expression correlated with worse prognosis, while other studies suggest potential benefits from anti-androgen therapies. This variability in outcomes highlights the complexity of TNBC and the need for further research to clarify the prognostic significance of this marker (51, 52).

In summary, *BRCA1/2* mutations and high TIL levels consistently emerged as positive prognostic factors, while markers such as elevated Ki-67 expression and *TP53* mutations generally indicated poorer outcomes. This understanding of prognostic factors is key to developing personalized treatment strategies and improving patient outcomes in TNBC (53).

3. Therapeutic Implications of Molecular Classification

The review has highlighted the therapeutic implications of molecular classification in TNBC, emphasizing the need for subtype-specific treatment approaches. The findings suggest that BL TNBC, due to its poor prognosis and aggressive nature, may require more intensive treatment regimens, including the addition of targeted agents or the use of neoadjuvant chemotherapy (54-56). M-subtype TNBC, on the other hand, may benefit from therapies targeting EMT pathways or from combinatorial approaches that modulate the TME. IM TNBC has emerged as a promising candidate for immunotherapy. The addition of pembrolizumab to chemotherapy in the KEYNOTE-522 trial resulted in significantly improved pCR rates in TNBC patients, particularly in those with high PD-L1 expression (57, 58). These results highlight the potential of ICIs as a standard component of TNBC treatment, especially in patients with the IM-subtype. For LAR TNBC, anti-androgen therapies, such as bicalutamide or enzalutamide, may offer therapeutic benefits. However, the limited clinical data available necessitate further studies to validate these findings and to identify reliable biomarkers for selecting patients who may respond to androgen receptor-targeted therapies (59, 60). The inclusion of LAR TNBC in clinical trials evaluating anti-androgen agents is essential to establish their role in the treatment of this subgroup (61).

This systematic review and meta-analysis have provided comprehensive insights into the prognostic significance and molecular classification of TNBC, which has emerged as a heterogeneous disease with distinct molecular subtypes, each carrying different prognostic implications and therapeutic vulnerabilities. The BL subtype, while being the most common, consistently demonstrates the poorest survival outcomes, with HRs indicating significantly increased risk of both death and disease recurrence. In contrast, the IM subtype shows more favorable outcomes, suggesting the important role of immune system engagement in TNBC prognosis.

The presence of specific molecular markers significantly influenced patient outcomes. *BRCA1/2* mutations, contrary to traditional assumptions about genetic mutations, actually confer a survival advantage with HRs of 0.68 for OS and 0.72 for DFS. This finding is particularly relevant given the availability of targeted therapies, such as PARP inhibitors for this subset of patients. The presence of high levels of TILs and PD-L1 expression emerged as positive prognostic indicators, particularly relevant in the era of immunotherapy.

The therapeutic landscape for TNBC has evolved to reflect these molecular classifications, with specific strategies showing efficacy in different subtypes. Platinum-based chemotherapy and PARP inhibitors demonstrate particular effectiveness in *BRCA*-mutated cases, while ICIs show promise in patients with high PD-L1 expression or elevated TILs. The development of ADC represents a significant advance in targeting specific molecular features of TNBC.

However, the review also highlighted the continuing challenges in treating non-BL TNBC subtypes, where response to current therapies remains suboptimal. The heterogeneity in survival outcomes across different molecular subtypes, as evidenced by the varying HRs, underscores the critical importance of molecular classification in treatment selection and prognostication. This suggests that future therapeutic approaches should increasingly focus on personalized strategies based on molecular subtyping and specific prognostic factors, rather than treating TNBC as a single entity.

Current Gaps and Future Directions

Despite the advances in understanding TNBC molecular subtypes and their therapeutic implications, several knowledge gaps remain. The lack of consensus on molecular classification criteria and the heterogeneity in the methodologies used to define TNBC subtypes across studies pose challenges in translating these findings into clinical practice. The development of standardized classification systems and high-throughput technologies, such as NGS, are needed to refine TNBC subtyping and identify novel therapeutic targets. Another critical gap is the limited understanding of resistance mechanisms in TNBC. While therapies such as PARP inhibitors and ICIs have shown promise in specific subgroups, resistance to these agents remains a significant hurdle. Research into the molecular mechanisms underlying resistance, including alterations in DNA repair pathways and immune evasion strategies, is necessary to develop combinatorial approaches to overcome resistance and improve outcomes for TNBC patients. Furthermore, the paucity of clinical trials evaluating novel agents in non-BL TNBC subtypes highlights the need for more inclusive research efforts. Given the distinct biological behavior of these subtypes, future clinical trials should incorporate molecular stratification to ensure that the unique therapeutic needs of each TNBC subtype are addressed. Identifying novel biomarkers predictive of treatment response will be important for guiding patient selection and personalizing therapy in TNBC.

The systematic review of the prognostic significance and molecular classification of TNBC highlighted the complexity and heterogeneity of this aggressive subtype of breast cancer. The analysis showed that TNBC is not a uniform disease but consists of multiple distinct molecular subtypes, BL, M, IM, and LAR, each with unique clinical features, prognostic outcomes, and therapeutic vulnerabilities. The BL- and M-subtypes were associated with poor prognosis and limited response to conventional therapies, while the IM subtype exhibited a more favorable prognosis and heightened sensitivity to immunotherapy. The least common subtype, LAR TNBC, on the other hand, remains an area requiring further investigation to better understand its clinical implications and therapeutic opportunities. Despite recent advances, significant challenges persist in the management of TNBC. The lack of targeted therapies for most TNBC subtypes, coupled with the high incidence of drug resistance and disease recurrence shows the need for further research to identify novel therapeutic targets and develop more effective treatment strategies. Future studies should focus on refining molecular subtyping through standardized criteria, exploring biomarkers for predicting treatment response and addressing resistance mechanisms to improve patient outcomes. Integrating molecular classification into clinical practice holds promise for the personalized treatment of TNBC. By tailoring therapeutic approaches based on the molecular profile of each TNBC subtype, it is hoped that the survival outcomes and quality of life of patients diagnosed with this challenging disease can be significantly improved.

Footnotes

Authorship Contributions

Concept: A.K.D.; Design: A.P.; Data Collection or Processing: S.G., M.G.; Analysis or Interpretation A.K.D., A.P.; Literature Search: A.K.D.; Writing: A.K.D.

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