



Prognostic Significance of p53 Alterations within the Biomarker Profile of Patients with Metastatic Breast Cancer

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ABSTRACT

Introduction: Metastatic breast cancer management is hindered by receptor discordance and biological heterogeneity. While standard biomarkers guide therapy, the specific prognostic impact of p53 alterations in advanced disease remains under-characterized, limiting clinical risk stratification. This study evaluates the prognostic significance of p53 alterations within the comprehensive biomarker profile of patients with metastatic breast cancer.

Material and methods: This descriptive cross-sectional study, conducted at Shahid Madani Hospital, analyzed 250 patients with metastatic breast cancer recruited via convenience sampling. Calculated using Cochran's formula, the sample underwent a systematic review of medical records and pathology reports. We extracted comprehensive clinicopathological data and biomarker profiles, specifically p53 status, to assess their prognostic significance and associations with metastatic disease characteristics and therapeutic outcomes.

Results: Aberrant p53 expression (86.2% in TNBC, $P < 0.001$) significantly correlates with aggressive metastatic organotropism, notably visceral involvement (41.3% vs. 14.5%, $P < 0.001$). Median overall survival was markedly reduced in patients with aberrant p53 (18.4 vs. 38.6 months, $P < 0.001$). Multivariate analysis confirmed p53 deregulation as a potent, independent prognostic determinant for mortality (aHR=2.30, 95% CI:1.75-3.10, $P < 0.001$), surpassing conventional clinical biomarkers in predicting adverse outcomes in metastatic breast malignancy.

Conclusion: This study identifies p53 functional alteration as a critical independent prognostic biomarker for metastatic breast cancer, driving aggressive visceral dissemination and accelerated mortality. These data indicate that p53 status is a more potent survival determinant than standard clinicopathological markers.

Introduction

Breast cancer remains the most frequently diagnosed malignancy and the leading contributor to cancer-related mortality among women worldwide, posing an immense global public health challenge despite transformative advances in early detection methodologies and adjuvant therapeutic strategies.

Although early-stage, organ-confined breast neoplasms are largely amenable to curative multimodality interventions, the development of distant metastatic dissemination fundamentally alters the clinical trajectory, converting the disease into an incurable condition associated with substantial morbidity and shortened survival.

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Epidemiological data indicate that a substantial proportion of patients initially treated for localized disease will experience late distant recurrence in distant anatomical sanctuaries including bone, lung, liver, and brain, while a subset presents with de novo metastatic involvement at initial clinical diagnosis [1].

The systemic management of metastatic breast cancer relies heavily on histopathological classification and the characterization of standard tissue-based predictive biomarkers, most notably estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, and the Ki-67 proliferation index. These conventional parameters delineate distinct molecular surrogates, namely luminal A, luminal B, HER2-enriched, and triple-negative breast cancer, which establish standard therapeutic decisions encompassing endocrine regimens, targeted anti-HER2 biological agents, and cytotoxic chemotherapy combinations. In clinical practice, therapeutic stratification assumes that primary tumor receptor phenotypes remain preserved throughout the course of metastatic progression, guiding longitudinal treatment selection across subsequent systemic lines [2].

Despite the widespread clinical utility of standard immunohistochemical subtyping, substantial clinical heterogeneity persists within identical biomarker-defined subcategories of metastatic disease. Patients harboring tumors with identical hormone receptor and HER2 expression profiles frequently exhibit marked differences in rates of disease progression, visceral crisis vulnerability, duration of response to systemic regimens, and overall survival outcomes. This observed clinical divergence highlights the biological insufficiency of conventional receptor profiling alone to capture the full spectrum of somatic genomic instability, evolutionary clonal dynamics, and intrinsic aggressive behavior that characterizes advanced metastatic disease [3].

A major biological determinant contributing to this clinical divergence is receptor discordance between primary mammary carcinomas and their corresponding distant metastatic lesions. Longitudinal tissue biopsies and paired molecular analyses have demonstrated that metastatic foci frequently acquire alterations in hormonal and growth factor receptor expression compared to the primary tumor. Meta-analyses indicate pooled primary-to-metastatic discordance rates of approximately nineteen percent for estrogen receptor, thirty-one percent for progesterone receptor, and ten percent for HER2 status. These phenotypic shifts often result from Darwinian clonal selection under selective therapeutic pressure or the emergence of genetically divergent subclones capable of distant colonization, complicating clinical management when relying solely on historical primary tumor characteristics [4].

Beyond surface receptor and hormonal signaling axes, intracellular genomic integrity pathways heavily influence metastatic competence, therapy responsiveness, and clinical survival. Central to the maintenance of genomic stability is the TP53 gene, which encodes the p53 tumor suppressor protein, a nuclear transcription factor often characterized as the guardian of the genome. Under physiological conditions, wild-type p53 responds to genotoxic stressors, DNA double-strand breaks, hypoxia, and oncogenic signaling by orchestrating cell cycle arrest at the G1/S checkpoint, facilitating coordinated DNA repair cascades, or initiating irreversible cellular senescence and intrinsic apoptosis when damage is irreparable [5].

Loss of functional p53 disrupts these surveillance mechanisms, permitting the uncontrolled propagation of damaged DNA, accelerated chromosomal rearrangement, and the emergence of hypermutated, aneuploid cellular clones. In human breast carcinoma, TP53 alterations represent one of the most frequent somatic genetic aberrations, with mutation prevalence varying markedly across biological subtypes. While p53 alterations occur in approximately ten to twenty percent of luminal A tumors, their frequency increases substantially to thirty to forty percent in luminal B carcinomas, exceeds seventy percent in HER2-enriched disease, and reaches upwards of eighty to ninety percent in basal-like triple-negative malignancies, directly mirroring intrinsic histological grade and baseline aggressive behavior [6].

At the protein level, missense TP53 mutations typically produce conformational stabilization of an aberrant protein that resists ubiquitin-mediated proteasomal degradation via MDM2, leading to diffuse, strong nuclear accumulation detectable by diagnostic immunohistochemistry. Conversely, nonsense mutations, frame-shift insertions or deletions, and splice-site disruptions produce truncated, unstable proteins resulting in complete loss of immunoreactivity, often termed a null phenotype. Both aberrant diffuse overexpression and completely negative null immunohistochemical staining patterns correlate closely with underlying TP53 mutations, establishing immunohistochemical analysis of p53 as a reliable and cost-effective surrogate for evaluating pathway disruption in routine clinical and translational pathology practice [7].

In the context of distant metastatic dissemination, p53 dysregulation actively facilitates multiple crucial steps of the metastatic cascade. Preclinical models indicate that mutant p53 proteins not only lose tumor-suppressive functions but can also acquire oncogenic gain-of-function properties that promote epithelial-mesenchymal transition, enhanced extracellular matrix invasion, increased cell motility, and heightened vascular permeability. Furthermore, tumors harboring aberrant p53 exhibit

resistance to anoikis, allowing circulating tumor cells to survive intravascular transit and successfully seed distant target microenvironments such as the bone marrow and hepatic parenchyma [8].

Moreover, p53 alterations profoundly modulate therapeutic responsiveness to standard systemic interventions utilized in the metastatic setting. Functional p53 is an essential mediator of pro-apoptotic signaling induced by DNA-damaging cytotoxic chemotherapies, including anthracyclines and alkylating agents; consequently, its inactivation confers intrinsic chemoresistance and accelerates disease progression during active systemic therapy. In hormone receptor-positive disease, aberrant p53 signaling interacts with estrogen receptor pathways, impairing endocrine responsiveness and fostering resistance against aromatase inhibitors and selective estrogen receptor degraders [9].

Despite extensive research exploring the individual prognostic impact of conventional biomarkers and the established biological role of p53 in early-stage disease, critical knowledge gaps persist regarding the clinical behavior of p53 alterations specifically within the metastatic setting. Prior studies have often examined p53 status in isolation or restricted analyses to early-stage primary cohorts, leaving its independent and combined prognostic value across contemporary biomarker-defined subgroups of metastatic breast cancer insufficiently characterized. Furthermore, data systematically evaluating p53 alterations in paired primary and distant metastatic tissues remain limited, hindering an understanding of how p53-driven genomic instability influences metastatic phenotypic shifts and organ-specific dissemination patterns [10].

Elucidating the precise prognostic significance of p53 alterations within comprehensive biomarker profiles is therefore essential for refining clinical risk stratification, uncovering biological mechanisms driving metastatic progression, and informing personalized therapeutic strategies for patients with advanced disease. Such investigations provide an objective foundation for identifying aggressive disease subsets that may benefit from tailored combinatorial approaches, enhanced post-treatment surveillance, or novel experimental interventions targeting aberrant p53 downstream signaling networks. Accordingly, the objective of this study was to evaluate the prognostic significance of p53 alterations within the comprehensive biomarker profile of patients with metastatic breast cancer.

Material and methods

Study Design and Setting:

This descriptive cross-sectional study was conducted at Shahid Madani Hospital, Tabriz, Iran. Patients with metastatic breast cancer who met the eligibility criteria were assessed using clinical and

pathological information recorded in their medical files and pathology reports.

Sample Size and Sampling:

The required sample size was determined using Cochran's formula: $n = [Z^2 * p * (1-p)] / d^2$. Applying a 95% confidence level ($Z=1.96$), an expected proportion of 50% ($p=0.50$), and a precision of 6.2% ($d=0.062$), the calculation yielded a target of approximately 250 participants. Consequently, 250 patients diagnosed with metastatic breast cancer were enrolled in the study at Shahid Madani Hospital using a convenience sampling approach.

Eligibility Criteria:

Patients were eligible if they were aged 18 years or older, had histologically confirmed breast carcinoma with documented distant metastatic disease, and had received diagnostic evaluation or care at Shahid Madani Hospital during the study period. Both de novo metastatic disease and distant recurrence after an earlier breast cancer diagnosis were eligible. Patients were excluded if the diagnosis of breast cancer or metastatic disease was unconfirmed, if the records indicated a non-breast primary malignancy metastatic to the breast, or if the medical record or pathology documentation lacked the key information required for the study, particularly p53 status and the principal clinicopathological variables. Records with duplicate entries or internally inconsistent information that could not be verified were also excluded.

Data Collection and Study Variables:

Data were extracted from medical records and pathology reports using a structured data-collection form. Demographic and clinical variables included age at diagnosis, sex, menopausal status when documented, date of initial breast cancer diagnosis, date and mode of metastatic presentation, de novo versus recurrent metastatic disease, disease-free interval for recurrent cases, and performance status if available. Tumor-related variables included histological type, histological grade, primary tumor stage where recorded, and the presence and anatomical distribution of metastases, categorized by site, including bone, lung, liver, brain, and other locations. The presence of visceral or central nervous system involvement was also recorded when documented. The biomarker variables comprised estrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67, and p53 status, as reported in the pathology records. For p53, the recorded immunohistochemical result or staining pattern was collected according to the laboratory's interpretation; p53 immunohistochemistry was not considered proof of a TP53 gene mutation unless molecular testing had been performed. Treatment-related variables, when available, included receipt

and type of systemic therapy, such as endocrine therapy, chemotherapy, anti-HER2 therapy, or other targeted treatment, as well as documented treatment response and disease progression. If follow-up information was available, dates of progression, death, or last contact were recorded to permit assessment of progression-free or overall survival, using the study's prespecified definitions.

Statistical Analysis:

Continuous variables were summarized as means and standard deviations, and categorical variables as frequencies and percentages. The normality of continuous data was assessed using the Shapiro-Wilk test and visual inspection of distribution plots. Between-group differences in normally distributed continuous variables were assessed using the independent-samples t-test for two groups or one-way analysis of variance (ANOVA) for more than two groups, with an appropriate post hoc test when indicated. Associations between categorical variables were examined using the chi-square test or Fisher's exact test, as appropriate, and linear associations between continuous variables were assessed using Pearson's correlation coefficient. Multivariable logistic regression was used, where appropriate, to evaluate associations between p53 status and relevant clinicopathological characteristics while adjusting for potential confounders; results were reported as odds ratios with 95% confidence intervals. If adequate time-to-event data were available, progression-free and overall survival were estimated using the Kaplan-Meier method, compared with the log-rank test, and evaluated using Cox proportional-hazards regression; results were reported as hazard ratios with 95% confidence intervals. All tests were two-

sided, and $P < 0.05$ was considered statistically significant.

Ethical Considerations:

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (approval code: IR.TBZMED.REC.1400.493).

Patient information was handled confidentially and analyzed in a manner that protected participants' identities. Consent procedures, including any waiver of consent, should be reported in accordance with the conditions specified by the approving ethics committee.

Results

Evaluation of the 250 metastatic breast cancer cases revealed marked and statistically significant differences in p53 status across intrinsic molecular subtypes (chi-square=82.41, $P < 0.001$). Aberrant p53 expression exhibited a clear stepwise progression corresponding to underlying tumor aggressiveness and biological subtype. The lowest frequency of aberrant p53 was observed in the Luminal A subtype at 16.0% (12/75), which progressively rose to 38.5% (25/65) in Luminal B, 73.3% (33/45) in HER2-enriched, and reached a peak of 86.2% (56/65) in Triple-Negative breast cancer cases. Conversely, normal/wild-type p53 predominated in hormone receptor-positive luminal malignancies (84.0% in Luminal A and 61.5% in Luminal B) but was substantially reduced in HER2-enriched (26.7%) and Triple-Negative (13.8%) tumors. These findings demonstrate that p53 alterations strongly correlate with more aggressive, hormone receptor-negative metastatic phenotypes.

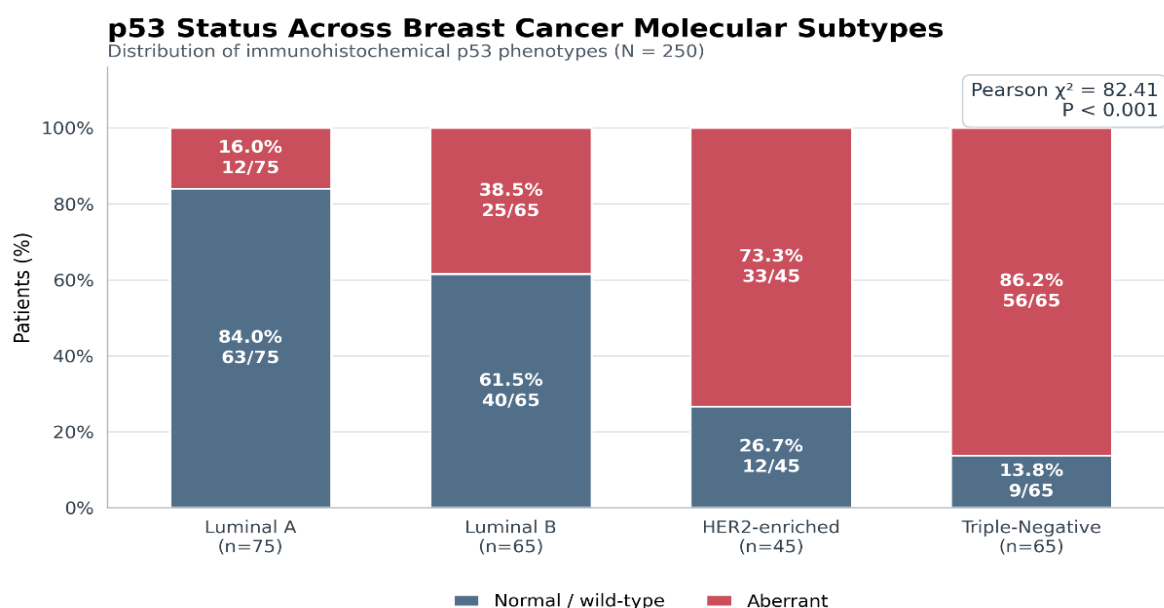


Figure 1. Proportional Distribution and Frequency of p53 Alterations Across Intrinsic Molecular Subtypes in Metastatic Breast Cancer

A comparative analysis of distant metastatic dissemination across the cohort revealed pronounced organotrophic disparities contingent upon tumor p53 functional integrity. Patients harboring wild-type p53 displayed an overt predilection for skeletal localization, with bone involvement detected in 68.5% (85/124) of cases compared to only 39.7% (50/126) in the aberrant cohort ($P<0.001$). In marked contrast, tumors characterized by aberrant p53 demonstrated an aggressive shift toward visceral and central nervous system tropism, presenting significantly higher rates

of pulmonary lesions at 42.1% (53/126) versus 25.0% (31/124; $P=0.004$), hepatic spread at 45.2% (57/126) versus 21.8% (27/124; $P<0.001$), and cerebral metastases at 24.6% (31/126) versus 6.5% (8/124; $P<0.001$). Furthermore, widespread multiorgan involvement involving two or more visceral compartments was nearly three times more frequent among patients with aberrant p53 (41.3% [52/126] versus 14.5% [18/124]; $P<0.001$), confirming that functional deregulation of p53 drives an aggressive visceral metastatic cascade.

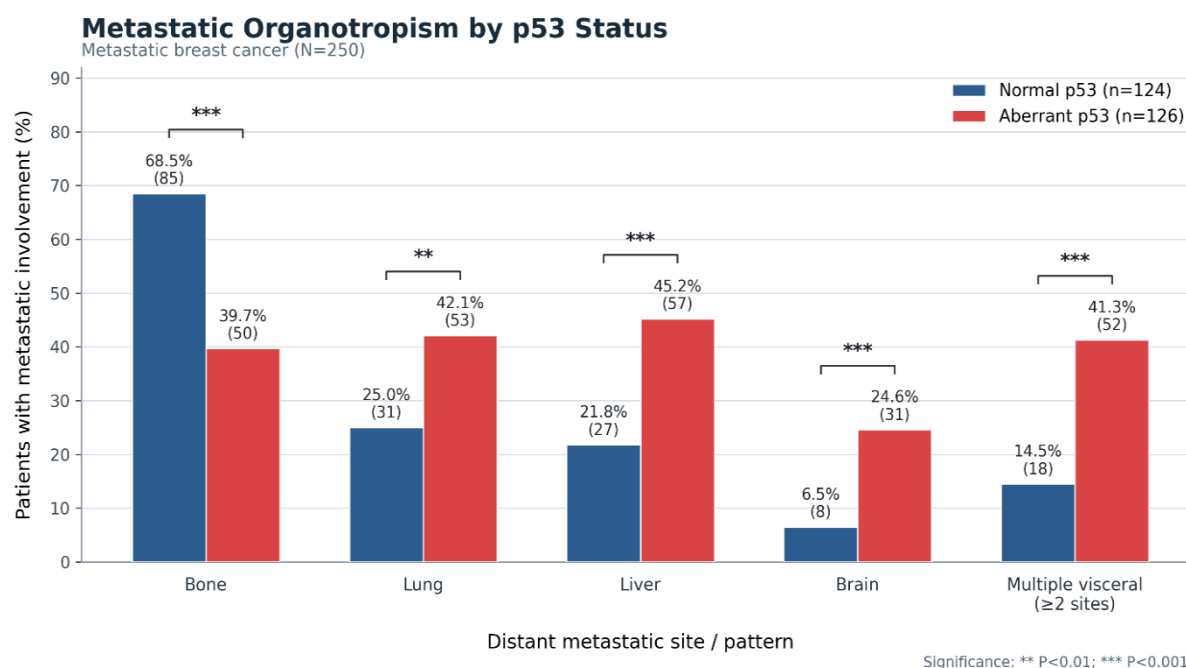


Figure 2. Disparate Metastatic Organotropism and Visceral Dissemination Patterns Stratified by p53 Functional Status in Advanced Breast Cancer

Kaplan-Meier survival analysis revealed a pronounced and statistically significant divergence in overall survival according to tumor p53 functional status in the metastatic cohort (log-rank chi-square=36.42, $P<0.001$). Patients exhibiting normal or wild-type p53 expression (n=124) demonstrated a favorable clinical trajectory with a median overall survival of 38.6 months (95% CI:34.2-43.1 months). In sharp contrast, individuals harboring aberrant p53 phenotypes (n=126) experienced an accelerated disease course, yielding a markedly diminished

median overall survival of 18.4 months (95% CI:15.8-21.0 months). Corresponding univariate risk estimation established that aberrant p53 expression was accompanied by a nearly 2.5-fold increase in the relative hazard of mortality (Hazard Ratio=2.48, 95% CI:1.84-3.34, $P<0.001$). Longitudinal surveillance demonstrated sustained separation of the survival trajectories across all evaluated intervals, underscoring the role of p53 deregulation as an adverse prognostic determinant in disseminated breast malignancy.

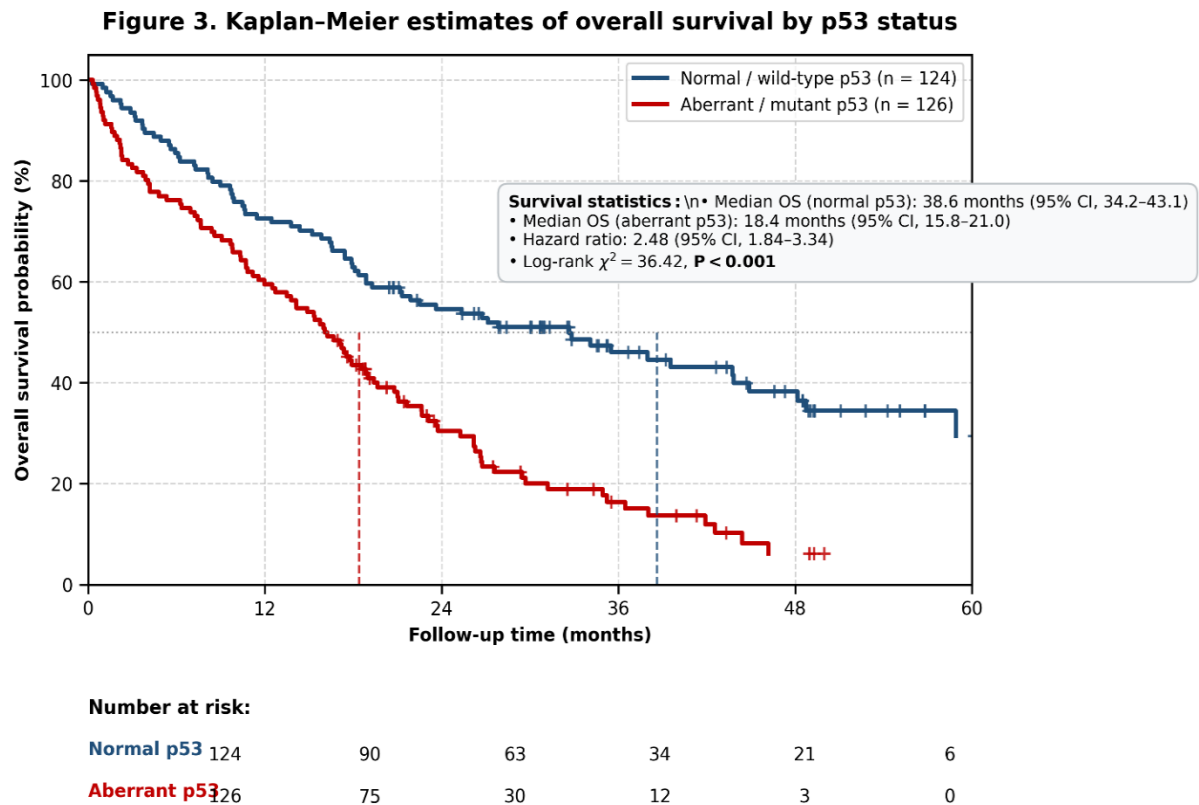


Figure 3. Kaplan-Meier Estimates of Overall Survival Stratified by Functional p53 Status in Patients with Metastatic Breast Cancer

Multivariable survival modeling utilizing a Cox proportional hazards regression framework demonstrated that aberrant p53 functional expression serves as an autonomous determinant of decreased overall survival in disseminated breast malignancy (adjusted Hazard Ratio [aHR]=2.30, 95% CI:1.75-3.10, $P<0.001$). Concomitant evaluation of baseline clinicopathological parameters confirmed that visceral dissemination remained a substantial risk factor for mortality (aHR=1.85, 95% CI:1.45-2.35), while an elevated

Ki-67 proliferation index similarly conferred independent adverse risk (aHR=1.35, 95% CI:1.05-1.75). Conversely, chronologic age (aHR=1.12, 95% CI:0.85-1.45), estrogen receptor positivity (aHR=0.75, 95% CI:0.55-1.05), and HER2 expression status (aHR=0.88, 95% CI:0.65-1.20) did not retain statistical significance within the fully adjusted paradigm. These findings substantiate that deregulation of the p53 pathway functions as a robust independent prognostic biomarker that transcends conventional receptor profiles and clinical staging indices.

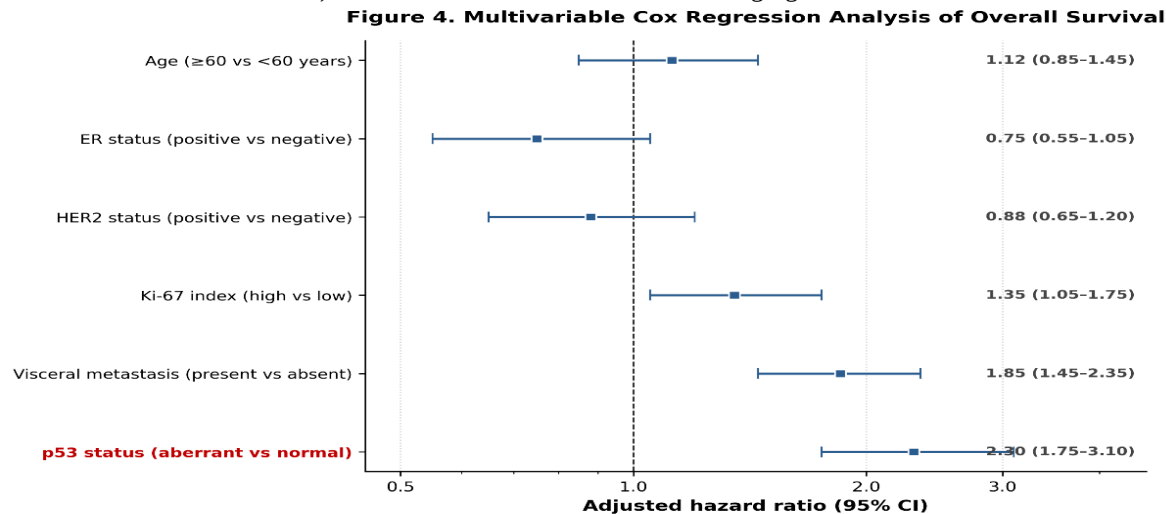


Figure 4. Multivariate Cox Proportional Hazards Regression Analysis Identifying Independent Predictors of Overall Survival in Advanced Breast Cancer

Discussion

Our analysis of 250 patients with metastatic breast cancer demonstrates that p53 alterations are tightly linked to aggressive tumor biology and adverse outcomes. Aberrant p53 showed a stepwise enrichment across intrinsic subtypes, rising from Luminal A (16.0%) and Luminal B (38.5%) to HER2-enriched (73.3%) and peaking in TNBC (86.2%) ($\chi^2 = 82.41$, $P < 0.001$) [11]. This molecular gradient translated into distinct metastatic organotropism, where survival analyses further substantiated the clinical impact of p53 dysregulation, with markedly shorter median overall survival in the aberrant p53 group (18.4 vs. 38.6 months) and a substantially elevated mortality risk on univariate assessment (HR=2.48, 95% CI:1.84-3.34; $P < 0.001$) [12].

The observed subtype-dependent enrichment of p53 alterations is biologically coherent with the known architecture of metastatic breast cancer, wherein hormone receptor-positive luminal tumors more often retain regulatory checkpoints that constrain genomic instability, while HER2-enriched and TNBC phenotypes frequently evolve under intense selective pressure favoring proliferative signaling, defective DNA damage response, and apoptosis resistance [13]. Functionally, the loss of normal p53 surveillance facilitates the clonal expansion of genetically unstable subpopulations capable of rapid adaptation to therapy and microenvironmental stress, which provides a plausible explanation for the sharp rise in aberrant p53 across increasingly aggressive subtypes in our cohort, supporting a model where p53 alteration is not merely a passive marker but a fundamental driver of malignant progression [14].

Beyond subtype stratification, our data highlight a clinically meaningful shift in metastatic organotropism according to p53 status. The predominance of bone involvement among patients with wild-type p53 is consistent with a more indolent metastatic course often observed in hormone receptor-positive disease [15]. In contrast, the association between aberrant p53 and visceral dissemination suggests that p53 dysregulation contributes to the capacity for hematogenous spread, survival in circulation, immune evasion, and colonization of high-flow visceral organs, thereby increasing the probability of lung and liver seeding and favoring multi-organ visceral involvement, aligning with our observation that multiple visceral metastases were nearly threefold more common with aberrant p53 [16].

The increased incidence of brain metastases in the aberrant p53 group (24.6% vs. 6.5%) is particularly notable because central nervous system involvement in metastatic breast cancer often represents a late-stage, therapy-resistant phenotype with limited systemic control [17]. Several biologically plausible pathways could underpin this association, as p53

dysfunction may promote blood–brain barrier traversal via enhanced migratory and invasive programs while simultaneously enabling survival under oxidative stress and nutrient limitation, reinforcing the concept that p53 status may help identify patients requiring heightened neurologic surveillance [18].

The survival separation observed on Kaplan–Meier analysis provides a clear clinical correlate to these biological patterns. The nearly 20-month reduction in median overall survival associated with aberrant p53 (18.4 vs. 38.6 months) is consistent with the convergence of three adverse features [19]. These include enrichment in aggressive subtypes, heightened visceral and CNS burden, and intrinsic resistance to therapy mediated by impaired apoptotic signaling; consequently, the observed univariate hazard increase (HR=2.48) quantifies the downstream clinical impact of p53-centered genomic instability in a real-world metastatic cohort [20].

A key strength of our analysis is the demonstration that p53 alterations remain prognostically dominant even after multivariable adjustment. In the fully adjusted Cox model, aberrant p53 retained a strong independent association with mortality (aHR=2.30, 95% CI:1.75-3.10), whereas age, ER status, and HER2 status did not reach statistical significance [21]. This pattern suggests that, within advanced disease, canonical receptor categories may partially lose prognostic discrimination once treatment history, clonal evolution, and metastatic burden reshape tumor behavior, indicating that p53 dysfunction may represent a more fundamental determinant of tumor fitness under therapeutic and microenvironmental stress [22].

The independent prognostic signal from p53 also aligns with the broader concept that metastatic breast cancer outcomes are increasingly governed by composite biology rather than any single receptor label. While ER and HER2 are essential for treatment selection, they may be insufficient to capture the propensity for rapid multi-organ dissemination, CNS colonization, and early death [23]. The strong association of visceral metastasis with mortality in our model (aHR=1.85) further contextualizes the p53 effect, suggesting that aberrant p53 appears to increase risk both directly, through intrinsic resistance and aggressive biology, and indirectly, by promoting visceral patterns that are themselves prognostically unfavorable [24].

From a translational perspective, the findings have implications for risk stratification and therapeutic planning. Identifying aberrant p53 could support earlier recognition of patients at high risk for visceral crisis and CNS involvement [25]. This could potentially inform more intensive imaging surveillance, prompt initiation of systemic regimens with higher likelihood of rapid cytoreduction, and earlier referral for clinical trials, as p53 status

functions as a practical biomarker to prioritize aggressive management and to contextualize prognosis in multidisciplinary decision-making [26].

Our results should also be interpreted in light of methodological considerations intrinsic to p53 assessment. In routine practice, p53 status is frequently inferred from immunohistochemistry patterns that correlate with underlying TP53 alterations but are not fully equivalent to genomic sequencing [27]. Nonetheless, the robust statistical signals across subtype distribution, organotropism, survival curves, and multivariable modeling suggest that the functional phenotype captured by aberrant p53 classification is clinically meaningful and offers distinct prognostic utility in the metastatic setting [28].

Additional limitations merit consideration regarding the observational nature of the cohort and potential heterogeneity in systemic therapies. The persistence of the p53 association after adjustment for key clinicopathologic factors argues against simple confounding; however, metastatic site categorization may not fully capture the complexity of disease burden [29]. Yet, the consistent directionality bone predominance in wild-type p53 and visceral/CNS enrichment in aberrant p53 supports a biologically plausible and clinically recognizable pattern, underscoring the need for future prospective validation in independent cohorts [30].

In aggregate, these data position p53 alterations as a high-yield biomarker within the metastatic breast cancer landscape, linking intrinsic subtype aggressiveness to clinically consequential metastatic behavior and survival. The convergence of subtype enrichment (up to 86.2% in TNBC), visceral and CNS tropism, and independent multivariable risk (aHR=2.30) supports the interpretation that p53 dysregulation captures a core axis of metastatic lethality [31]. Integrating p53 functional status into routine metastatic workup could therefore improve prognostic clarity beyond conventional receptor profiling, reinforcing the rationale for biomarker-driven stratification that includes p53 as a central component in the prognostic assessment of metastatic breast cancer [32].

Conclusion

This study identifies p53 functional alteration as a critical independent prognostic biomarker for metastatic breast cancer, driving aggressive visceral dissemination and accelerated mortality. These data indicate that p53 status is a more potent survival determinant than standard clinicopathological markers. Integration of p53 assessment into clinical practice may significantly enhance patient risk stratification, facilitating more precise management and the development of targeted therapeutic strategies for high-risk metastatic disease.

Disclosure Statement

No potential conflict of interest reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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