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ORIGINAL RESEARCH

Genomic Insights Into Early Relapsed Breast Cancer: Prognostic Challenges and Mutation Landscape

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Purpose: Early relapsed breast cancer, characterized by recurrence within two years post-surgery, often results from drug resistance and rapid progression. The clinicopathological, prognostic and molecular features of these patients still await exploration.

Methods: In this study, 43 patients with early relapsed breast cancer were included as well as 42 advanced breast cancer patients who experienced a recurrence after two years since surgery as the control group. Clinicopathological factors and prognosis were compared among the two groups, and tumor tissue from 27 available early relapsed patients was subjected to genetic sequencing.

Results: Compared with the control group, early relapsed group exhibited more aggressive malignant biological characteristics, shorter median overall survival (27.8 vs 49.8 months, P=0.005) and lower objective response rate for the first line treatment (42.90% vs 86.8%, P<0.001). Genetic sequencing of 27 early relapsed breast cancer demonstrated with TP53 (52%), PIK3CA (22%), and MLL3 (19%) as the top three frequently mutated genes, suggesting potential therapeutic targets for personalized treatment strategies.

Conclusion: Early relapsed breast cancer patients demonstrated poor prognosis and treatment response, indicating a reagent need of effective treatment combination for disease control. Genetic sequencing may identify potential therapeutic targets, providing new therapeutic opportunities for such patients. These findings underline the urgent need for personalized therapeutic strategies informed by genetic profiling to improve outcomes for early-relapsed breast cancer patients.

Keywords: breast cancer, early relapse, clinicopathological characteristics, prognostic features, genetic sequencing

Introduction

There were 2.3 million newly diagnosed cases of breast cancer worldwide with 670,000 fatalities in 2022 as the fourth most significant contributor to global cancer-related fatalities.[1] With the continuous diversification of treatment methods, the prognosis for breast cancer patients has greatly improved. However, postoperative recurrence continues to be a significant concern. Approximately 30% of early-stage breast cancer patients will experience a recurrence. There is a peak in the rate of recurrence within two years after breast cancer surgery who were classified as having an "early relapse". Studies in Western populations report a similar early-relapse rate of approximately 15%, although variations are observed due to differing treatment protocols and genetic predispositions.[2] More early breast cancer patients relapse after two years since surgery who were considered as having a "normal relapse".

Previous research has shown that breast cancer patients who experienced early relapse had a higher proportion of hormone receptor negativity, a greater number of lymph nodes involvement, and a more unfavorable prognosis.[3,4] This reveals to us the critical situation of breast cancer patients with early recurrence from the perspective of clinical features. Certain pathological characteristics are associated related with specific genetic mutation patterns. High-grade tumors are

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frequently correlate with alterations in the TP53 pathway, while mutations in the PI3K/AKT pathway are more prevalent in hormone receptor-positive patients.[5,6] At the levels of molecular drivers and pathways, previous studies have revealed that the PI3K-AKT signaling pathway and TP53 mutations are frequently implicated in aggressive breast cancer phenotypes, highlighting the importance of these molecular targets in early recurrence. Nevertheless, it is important to conduct further investigation to determine if there are specific attributes that might be utilized to forecast early relapse. Patients with early-relapsed breast cancer frequently exhibit resistance to conventional treatments, including taxanes, endocrine therapy and radiation therapy, necessitating novel therapeutic strategies. Recent advances in targeted therapeutics, exemplified by the PI3K inhibitor Alpelisib for PIK3CA-mutated breast cancers, demonstrate promising clinical potential, although their efficacy in early-relapsed cases requires further investigation. Comprehensive genomic profiling has emerged as a powerful tool for identifying actionable mutations in these treatment-refractory patients, particularly those who have developed resistance to standard endocrine or HER2-targeted therapies. The identification and validation of robust prognostic biomarkers could enable risk stratification for early relapse, facilitating the implementation of more intensive treatment approaches in high-risk populations.

The cohort of this retrospective study covers a wide variety of patients in terms of age, hormone receptor status, and previous treatment regimens, reflecting the heterogeneity of early-relapsed breast cancer cases. The study aims to comprehensively analyze the clinicopathological and molecular characteristics of early recurrent metastatic breast cancer, examine its prognostic factors, and evaluate the efficacy of first-line treatment, trying to offer novel perspectives on the identification and management of early relapsed breast cancer.

Materials and Methods

Patients Inclusion and Follow-up

We systematically gathered clinical information from a cohort of 85 breast cancer patients who received treatment at Nanjing Drum Tower Hospital between January 2017 and April 2023. These patients were diagnosed with breast cancer based on pathological or imaging evidence and showed signs of recurrence or metastasis according to imaging results. The comprehensive clinicopathological information and follow-up records were extracted from electronic medical records of the patients.

The overall survival (OS) was defined as duration from recurrence or metastasis to the point of death or the end of follow-up period, while progression-free survival 1 (PFS1) was defined as the duration from the start of first-line treatment until the occurrence of tumour progression. The best overall response (BOR) refers to the highest level of response rate observed during the period from the start of first-line treatment until disease progression or relapse. The aforementioned evaluation was conducted by two oncologists based on the patient's imaging data. The median follow-up time for all patients was 29.4 months, with the data collection cutoff date being June 15, 2023.

Statistical Analysis

All analyses were done by the SPSS 27.0 and R 4.2.0 statistical software, and GraphPad Prism 7 was used for plotting. The chi-squared test was employed to compare the tumor characteristics of patients with early and normal relapse. Survival was evaluated by using Kaplan–Meier estimates and survival curves were compared by using the Log rank test. P-values were two-sided, and a P-value less than 0.05 was considered statistically significant for all statistical analyses.

Genetic Sequencing in Early Relapse Breast Cancer Tissue

Tumor tissues were available for 27 early relapse patients. All samples were formalin-fixed and paraffin-embedded (FFPE) and underwent targeted panel sequencing for the analysis of genetic alterations. Tumor DNA was extracted from FFPE tumor tissue specimens using the ReliaPrep FFPE gDNA Miniprep System (Promega). 300 to 800 ng DNA was sheared into fragments at a 200 to 250 bp peak with a Covaris S2 ultrasonicator (Covaris, Inc). And indexed NGS libraries were prepared using the NEBNext Ultra DNA Library Prep Kit for Illumina (NEB). Subsequently, the DNA libraries were hybridized with the 1021 gene panel, which is a targeted next-generation sequencing (NGS)-based diagnostic platform covering approximately 95% of solid tumor-related genes found in COSMIC and TCGA databases.

Finally, the hybridized libraries were sequenced using a 100bp paired-end configuration on a DNBSEQ-T7RS sequencer (MGI Tech, Beijing, China). The median effective depth of coverage in tissue was 600× (range, 200–2300×). The media tumor purity of FFPE sample was 0.41 (range, 0.22–0.68).

Raw data were filtered to remove adaptor and low-quality reads by fastp software (version. v0.23.2). Clean reads were aligned to the reference human genome hg19 using Burrows-Wheeler Aligner (BWA, version 0.7.12-r1039). Duplicated reads were marked and removed using the MarkDuplicates tool in Picard (version 4.0.4.0; Broad Institute) for tumor and germline genomic DNA. Single nucleotide variants (SNVs), copy number variants (CNVs) and structural variants (SVs) were identified by TNscope, CNVKit and NCsv2 respectively. All reliable gene variants were supported by at least 5 high-quality sequencing reads.

Functional Analysis of Mutant Genes in Early Relapsed Breast Cancer Tissue

The R (version 4.2.0) cluster Profiler package was used for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. This software package reveals the biological processes, cellular components, molecular functions, and pathways associated with the mutant genes in patients with early relapse.

Results

Early Relapsed Patients Have Worse Pathological Characteristics and Receive More Aggressive Adjuvant Therapy

A total of 85 patients with recurrent metastatic breast cancer were included in this study, comprising 43 cases in the early relapse group and 42 cases in the normal relapse group. The clinicopathological characteristics and adjuvant therapy profiles of both groups are presented in Table 1. Compared to the normal relapse group, the early relapse group showed significantly higher proportions of patients with extensive lymph node metastasis (N2-3: 53.5% vs 28.6%, p=0.020), high-grade tumors (WHO III vs WHO I-II: 62.8% vs 40.5%, p=0.040), low estrogen receptor (ER) expression (51.2% vs

Table 1 Characteristics of Patients with Recurrent Tumors

Characteristics	n	Early Recurrence (n=43)	Normal Recurrence (n=42)	P Value
Age				0.331
<50	40	18(41.9)	22(52.4)	
≥50	45	25(58.1)	20(47.9)	
Pathology type				0.210
Invasive ductal carcinoma	79	38(88.4)	41(97.6)	
Invasive lobular carcinoma	3	3(7.0)	0(0)	
Papillary carcinoma	2	1(2.3)	1(2.4)	
Basaloid carcinoma	1	1(2.3)	0(0)	
Primary tumour stage				0.475
T1	24	11(25.6)	13(31.0)	
T2	57	31(72.1)	26(61.9)	
T3	4	1(2.3)	3(7.1)	
Regional lymph node stage				0.020*
N0-1	50	20(46.5)	30(71.4)	
N2-3	35	23(53.5)	12(28.6)	
ER (%)				0.018*
<10	34	22(51.2)	11(26.2)	
≥10	51	21(48.8)	31(73.8)	
PR (%)				0.010*
<20	54	33(76.7)	21(50.0)	
≥20	31	10(23.3)	21(50.0)	

(*Continued*)

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Table 1 (Continued).

Characteristics	n	Early Recurrence (n=43)	Normal Recurrence (n=42)	P Value
Ki67 (%)				0.527
<20	14	6(14.0)	8(19.0)	
≥20	71	37(86.0)	34(81.0)	
HER2 status				0.222
Positive	29	12(27.9)	17(40.5)	
Negative	56	31(72.1)	25(59.5)	
Molecular typing				0.008*
HR+HER2-	33	13 (30.2)	20 (47.6)	
HER2+	29	12 (27.9)	17 (40.5)	
HR-HER-	23	18 (41.9)	5 (11.9)	
Histological grade				0.040*
I–II	41	16(37.2)	25(59.5)	
III	44	27(62.8)	17(40.5)	
Visceral metastasis				0.438
Yes	47	22(51.2)	25(59.5)	
No	38	21(48.8)	17(40.5)	
Visceral crisis				0.215
Yes	6	5(11.6)	1(2.4)	
No	79	38(88.4)	41(97.6)	
Organ of recurrence				
Bone metastasis	32	17(39.5)	15(35.7)	0.716
Chest wall metastasis	16	10(23.3)	6(14.3)	0.290
Lung/pleura metastasis	31	15(34.9)	16(38.1)	0.758
Liver metastasis	17	6(14.0)	11(26.2)	0.158
Brain metastasis	4	3 (7.0)	1 (2.4)	0.625
Number of organ metastasis				0.234
Single	44	25(58.1)	19(45.2)	
Multiple	41	18(41.9)	23(54.8)	
Adjuvant therapy				
Adjuvant chemotherapy	83	43(100)	40(95.2)	0.241
Radiotherapy	60	38(88.4)	22(52.4)	<0.001*
Trastuzumab for HER2+	22	10(23.3)	12(28.6)	0.576
Endocrine therapy for HR+	43	18(41.9)	25(59.5)	0.103

Note: Symbol * indicate p<0.05.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

26.2%, p=0.018), and low progesterone receptor (PR) expression (76.7% vs 50.0%, p=0.010). Regarding treatment modalities, a significantly higher percentage of patients in the early relapse group received radiotherapy (88.4% vs 52.4%, p<0.001). Additionally, molecular subtyping revealed a significant difference between the groups, with triple-negative breast cancer (TNBC) being more prevalent in the early relapse group (p=0.008). However, no significant differences were observed between the groups in terms of age, pathological type, metastatic sites, or other adjuvant treatments.

Early Relapsed Patients Show Poorer Treatment Response

First-line treatment strategies were comparable between the early relapse and control groups, with no significant differences in regimen selection (Table 2). However, treatment outcomes differed markedly between the groups. The early relapse group demonstrated a significantly shorter median progression-free survival (PFS1) of 8.2 months (95% CI: 4.9–11.5) compared to 17.8 months (95% CI: 11.2–24.4) in the control group (p=0.012) (Figure 1A), suggesting reduced drug sensitivity in early relapsing patients. Among the 73 patients with available radiological assessments (35 in the early

Table 2 First-Line Treatment Regimen of Two Groups of Patients

Treatment	n	Early Recurrence (n=43)	Normal Recurrence (n=42)	P Value
Chemotherapy				
Yes	56	26 (60.5)	30 (71.4)	0.286
No	29	17 (39.5)	12 (28.6)	
Trastuzumab for HER2+				
Yes	27	11 (25.6)	16 (38.1)	0.215
No	58	32 (74.4)	26 (61.9)	
Endocrine therapy for HR+				
Yes	28	16 (37.2)	12 (28.6)	0.397
No	57	27 (62.8)	30 (71.4)	

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

relapse group and 38 in the control group), the objective response rate to first-line treatment was significantly lower in the early relapse group (42.9% vs 86.8%, p<0.001) (Figure 1B). These findings collectively indicate that patients with early relapse exhibit notably diminished therapeutic responses to first-line treatment.

Patients in the Early Relapsed Group Have a Shorter Overall Survival

Overall survival (OS) analysis revealed significant differences between the groups. The early relapse group demonstrated a median OS of 27.8 months (95% CI: 17.6–38.0), substantially shorter than the control group's 49.8 months (95% CI: 36.6–63.0). Kaplan-Meier survival analysis further illustrated this disparity, with the early relapse group showing inferior survival rates at both 1-year (85.3% vs 97.3%) and 3-year (43.5% vs 69.5%) timepoints compared to the control group (p=0.005) (Figure 2).

Analysis of DNA Mutation Characteristics in Early Relapsed Breast Cancer

Genomic profiling was conducted on tumor specimens from early relapse breast cancer patients. Among the 27 available specimens, single nucleotide variants (SNVs) were detected in 96.3% (26/27) of cases, with a total of 167 mutations identified (mean: 6 mutations per patient). The mutation spectrum comprised predominantly missense mutations (88.5%, 23/26), followed by nonsense mutations (38.5%, 10/26) and frameshift mutations (26.9%, 7/26). The most frequently mutated genes were TP53 (52%), PIK3CA (22%), and MLL3 (19%), with SYK, RECQL4, and BRCA2 mutations each present in 11% of cases (Figure 3A). Copy number variations (CNVs) were observed in 92.6% (25/27) of samples, predominantly characterized by amplifications rather than deletions. The genes most commonly affected by CNVs

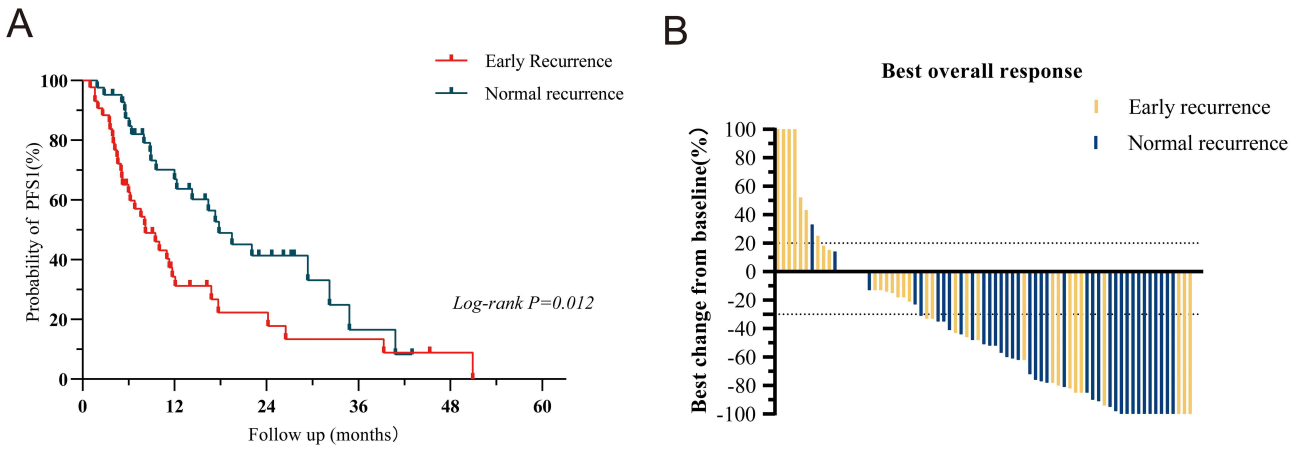

Figure 1 The efficacy of first-line treatment for the early relapsed group and the control group. (**A**) The Kaplan–Meier curves of PFS1 of two groups. (**B**) The BOR of two groups.

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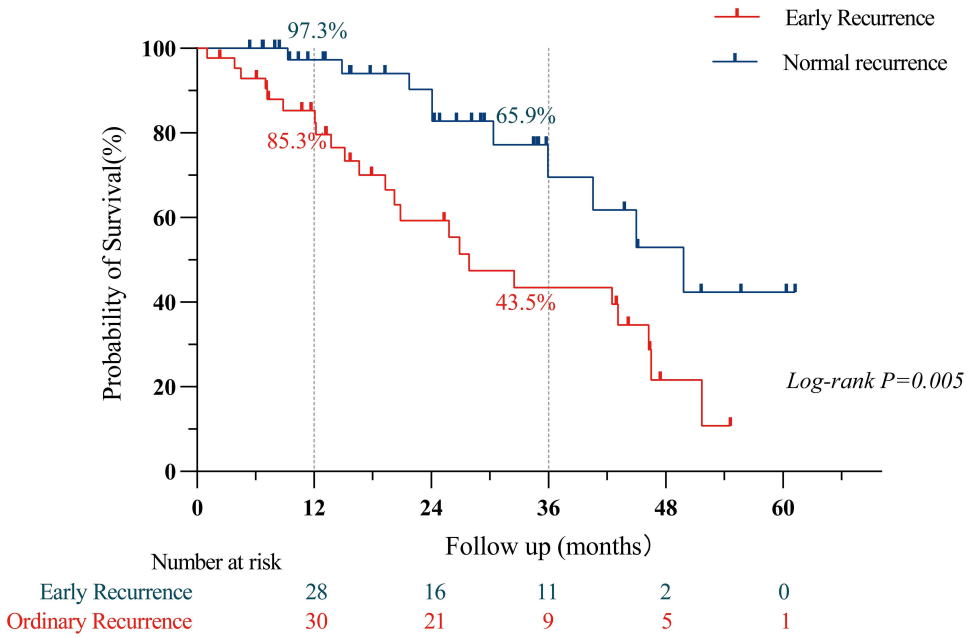

Figure 2 Kaplan–Meier overall survival curves comparing early-relapse (≤24 months) versus late-relapse (>24 months) breast cancer patients.

included MYC (59%), CDK4 (59%), CDKN1B (56%), MCL1 (56%), CCND1 (37%), and DAXX (30%) (Figure 3B). Additionally, the tumor mutational burden (TMB) averaged 6.17 mutations per megabase, and all 27 cases exhibited microsatellite stability.

Functional and Pathway Enrichment of Mutated Genes in Early Relapsed Breast Cancer Tissue

To elucidate the functional implications of mutated genes in early relapse breast cancer, we conducted comprehensive functional enrichment analyses using both Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) approaches. GO analysis revealed three major functional categories: In biological processes (BP), the mutated genes were predominantly associated with protein autophosphorylation, negative regulation of apoptotic processes, and positive regulation of cell population proliferation. Within cellular components (CC), these genes were primarily localized to receptor complexes, chromosomes, and telomeric regions. The molecular functions (MF) were mainly characterized by chromatin binding and protein kinase binding activities (Figure 3C). KEGG pathway analysis demonstrated significant enrichment in several key signaling cascades, including the PI3K-Akt signaling pathway, microRNA-mediated cancer pathways, and human papillomavirus infection-related pathways (Figure 3D).

Validation of the Relationship Between TOP20 Altered Genes in the Early Relapsed Group and Disease Progression and Prognosis Using the METABRIC Database

We analyzed survival outcomes in the METABRIC database by stratifying breast cancer patients based on genetic alterations. For SNV analysis, patients were categorized into two groups: those harboring mutations in the top 20 identified genes (Altered group) and those without such mutations (Unaltered group). Kaplan-Meier survival analysis revealed that the Altered group exhibited significantly worse overall survival (OS) ($p=0.012$) (Figure 4A) and earlier disease recurrence or metastasis ($p=0.032$) (Figure 4B).

A parallel analysis was conducted for CNVs, similarly dividing patients into Altered and Unaltered groups based on the presence of alterations in the top 20 genes. The Altered group demonstrated significantly inferior OS ($p<0.001$) (Figure 4C) and earlier disease recurrence ($p<0.001$) (Figure 4D). These findings from the METABRIC cohort align with our institutional data, demonstrating that alterations in these top 20 genes correlate strongly with accelerated disease progression and poor clinical outcomes.

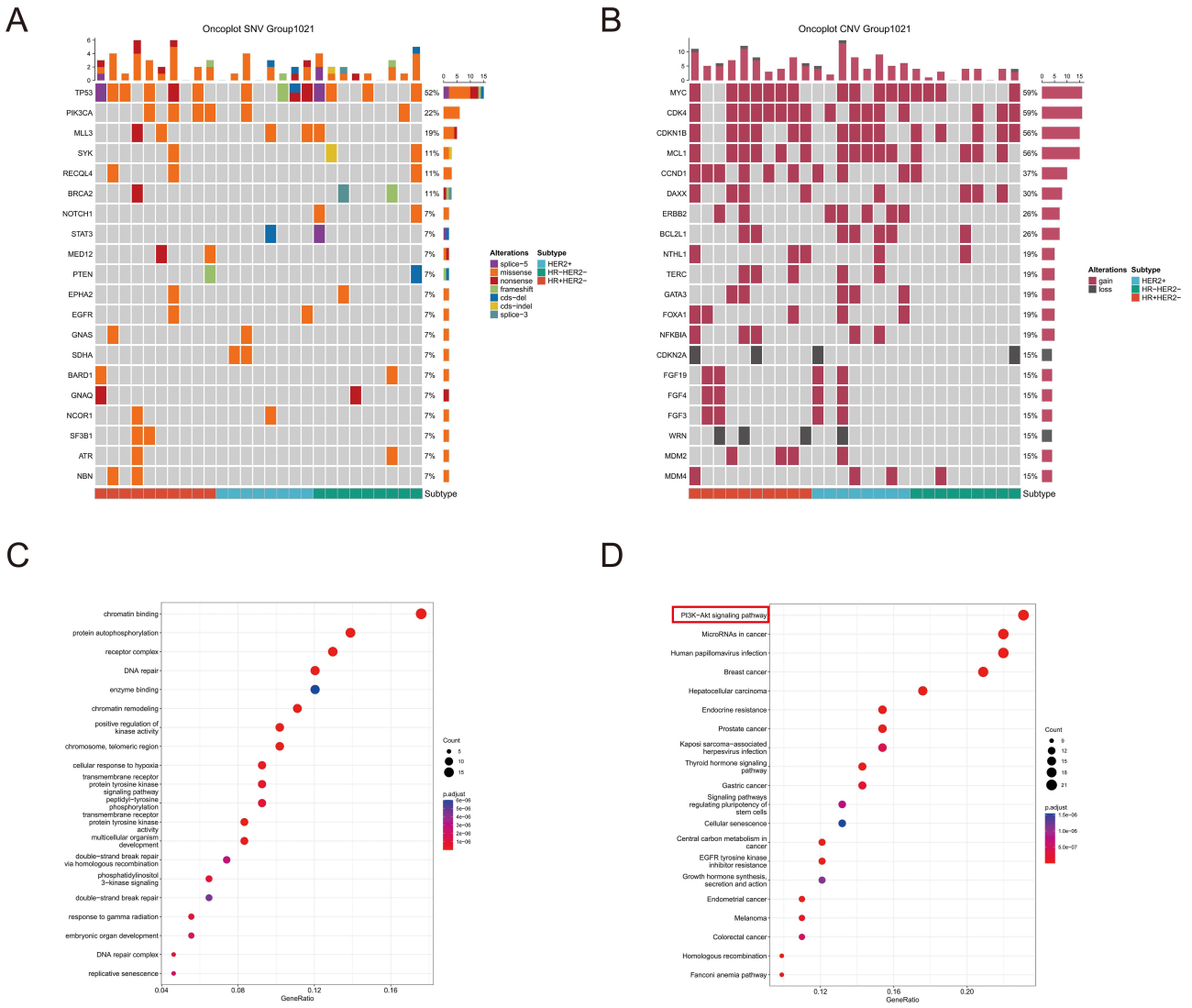

Figure 3 Functional and pathway enrichment of mutated genes in early relapsed breast cancer tissue. (**A**) Single nucleotide variant profiling of 27 samples of early relapsed group (top 20 frequent mutations). (**B**) Copy number variation of 27 samples of early relapsed group (top 20 frequent alterations). (**C**) GO enrichment analysis of mutated genes in early relapsed breast cancer. Size and color of the bubble represent the number of mutated genes enriched in a pathway, or biological process, and enrichment significance, respectively. (**D**) KEGG pathway enrichment analysis is summarized by bubble charts. The x-axis shows enrichment factors and the y-axis shows the pathway terms.

Notes: The PI3K - AKT pathway plays a crucial role in breast cancer. It is involved in regulating multiple cellular processes such as cell growth, survival, proliferation, and metabolism. Activation of this pathway can promote uncontrolled cell division, prevent apoptosis, and enhance cell motility, all of which contribute to the development, progression, and metastasis of breast cancer.

Discussion

The temporal patterns of recurrence and metastasis in early-stage breast cancer follow distinct characteristics. Our study revealed that patients with early recurrence or metastasis exhibited features associated with aggressive tumor biology, including advanced lymph node involvement and higher histological grade, consistent with previous findings.[3] This correlation between unfavorable tumor biology and accelerated disease progression typically manifests as earlier onset of recurrence and metastasis, resulting in a median overall survival approximately half that of patients with conventional recurrence patterns. Patients experiencing relapse or metastasis within two years post-surgery frequently demonstrate therapeutic resistance. A comprehensive real-world study, which defined early relapse as occurrence between 6–18 months post-surgery, demonstrated that early-relapsing patients presented with greater tumor burden, increased lymph node involvement, and significantly worse prognosis (median OS: 10.1 vs 17.1 months, $p<0.001$). These patients also showed diminished response to first-line therapy (median OS: 3.1 vs 5.3 months, $p<0.001$).[4] Additional research has corroborated these findings regarding poor treatment responses in early-relapsing patients.[5] Our findings align with these previous observations, demonstrating shorter median PFS1 and inferior response to first-line

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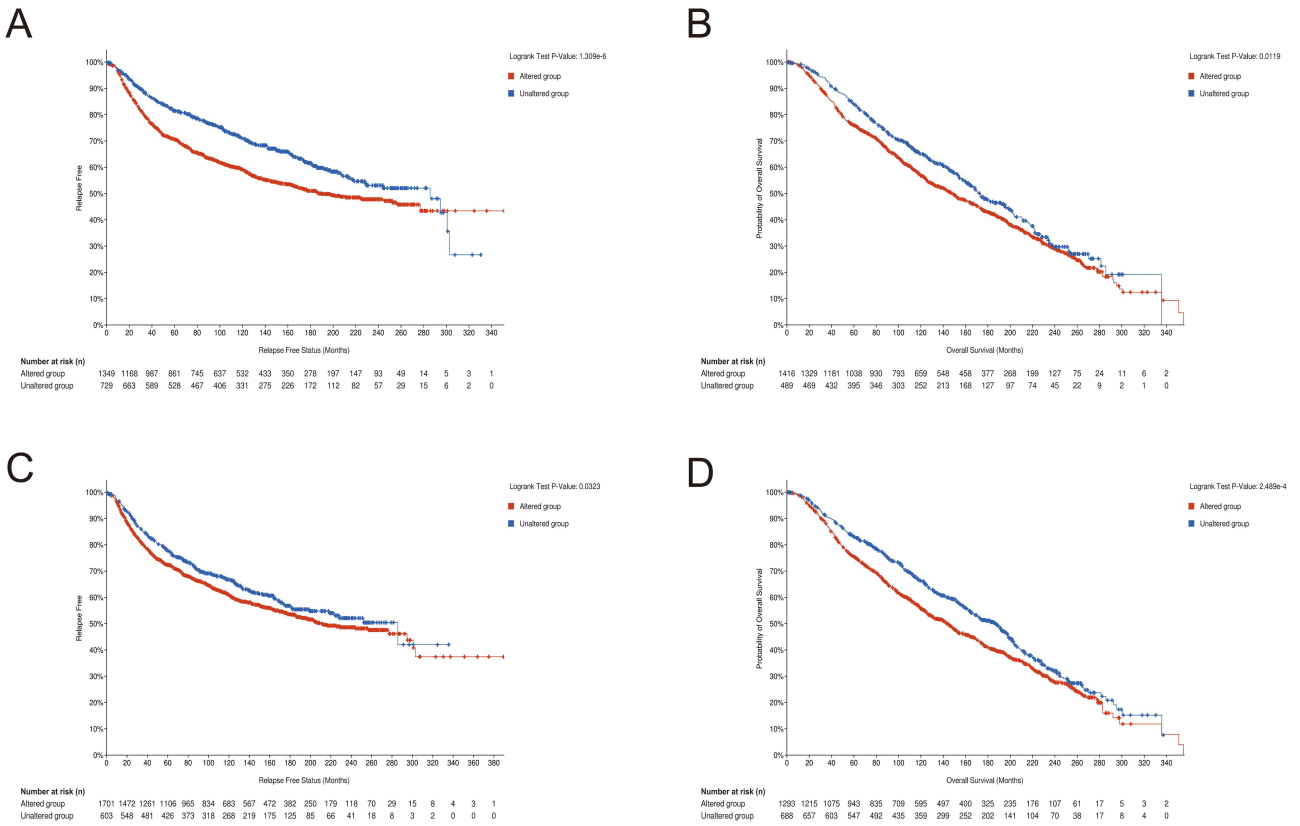

Figure 4 Validation of the relationship between TOP20 altered genes in the early relapsed group and disease progression and prognosis in the METABRIC database. (**A**) The Kaplan–Meier curves of OS of SNVs Altered group and Unaltered group in the METABRIC database. (**B**) The Kaplan–Meier curves of DFS of SNVs Altered group and Unaltered group in the METABRIC database.(**C**) The Kaplan–Meier curves of OS of CNVs Altered group and Unaltered group in the METABRIC database.(**D**) The Kaplan–Meier curves of DFS of CNVs Altered group and Unaltered group in the METABRIC.

treatment in early-relapsing breast cancer patients. These results underscore the substantial therapeutic challenges in managing early-relapsing breast cancer. Furthermore, disease progression shortly after adjuvant therapy completion strongly suggests potential treatment resistance. This clinical observation influences treatment selection: for instance, taxanes are typically avoided as first-line therapy in cases where disease progression occurs within one year of completing adjuvant chemotherapy.

Our study revealed a distinctive mutation profile in early-relapsing breast cancer patients, characterized by high frequencies of mutations in TP53 (52%), PIK3CA (22%), MLL3 (19%), SYK (11%), RECQL4 (11%), and BRCA2 (11%). This profile differs notably from the mutation spectrum previously reported in a comprehensive study of Chinese breast cancer patients, which identified TP53 (39.8%), PIK3CA (38.4%), GATA3 (10.3%), MAP3K1 (8.2%), KMT2C (also known as MLL3, 7.0%), and AKT1 (6.3%) as predominant mutations.[7] The early-relapsing cohort exhibited a more concentrated mutation spectrum with higher individual mutation frequencies compared to the general breast cancer population.

TP53, the most frequently mutated gene in breast cancer, showed a remarkably high mutation rate of 59% in our early-relapsing cohort, substantially exceeding the typical 27–37% observed in general breast cancer populations. This elevated frequency aligns with previous findings correlating TP53 mutations with poor prognosis.[8] Tumor suppressor and transcription factor in mammals. It can regulate processes such as the cell cycle and apoptosis, maintaining genomic stability.[9] Most p53 mutations occur in the DNA - binding domain. Hotspot mutations such as R248 and R273 are associated with tumor growth, drug resistance, and poor prognosis.[10] These mutations possess the oncogenic "gain - of - function" (GOF) property. The mutant p53 promotes cancer development by interfering with the activation of pro - apoptotic genes and assisting other transcription factors. Due to the stability of the p53 GOF mutant form, a strong p53 signal detected by immunohistochemistry indicates a highly invasive cancer and a poor prognosis for patients.[11]

PIK3CA mutations, occurring in 24–40% of breast cancer patients,[12] represent the second most common genetic alteration. Therapeutic approaches targeting PIK3CA mutations have shown promise, with FDA approval of PI3K inhibitors such as Alpelisib for HR-positive, HER2-negative breast cancer following endocrine therapy.[13,14] Novel approaches, including PIK3CA-

targeted antigen vaccines, are under active investigation.[15] MLL3 mutations have been shown to enhance tumor invasiveness both in vivo and in vitro,[16,17] and are associated with endocrine therapy resistance and poor clinical outcomes.[18] Notably, MLL3 mutations are frequently observed (28%) in PDL1-positive TNBC in Chinese populations.[19] The identification of a unique mutation spectrum, particularly the higher prevalence of TP53, PIK3CA, and MLL3 mutations in early-relapsed cases, contributes new genetic insights to the field.

The elevated mutation frequencies of SYK, RECQL4, and BRCA2 in early-relapsing patients exceed those typically observed in Chinese breast cancer populations. SYK expression in tumor cells promotes tumor progression and immunosuppression,[20] while RECQL4 and BRCA2 mutations compromise DNA repair and replication mechanisms, leading to genomic instability.[21,22] These findings suggest that mutations in MLL3, SYK, RECQL4, and BRCA2 may serve as molecular markers for accelerated disease progression.

The observed CNV patterns demonstrated distinct distributions across molecular subtypes, with triple-negative breast cancer (TNBC) exhibiting notably fewer CNVs. Among patients with early-recurrent breast cancer, MYC amplification emerged as the most frequent CNV, present in 59% of cases—a higher prevalence than the approximately 48% reported in general breast cancer populations.[23] The MYC gene product orchestrates multiple cellular processes and plays crucial roles in tumor initiation, progression, and therapeutic resistance, positioning it as a promising therapeutic target for early-recurrent disease.[24] Notably, MYC activates the VEGF signaling pathway, promoting tumor angiogenesis and disease progression.[25] The clinical significance of MYC amplification was demonstrated in a Phase II trial, where patients with MYC amplification showed superior pathological complete remission rates (76.9% vs 50.0%) when treated with combined antiangiogenic therapy and chemotherapy in the neoadjuvant setting.[26] A novel MYC-degrading compound A80.2HCl is under development and may represent a possible therapeutic option for early-recurrent breast cancer patients.[27] Other amplified related genes are mainly concentrated in the cell cycle pathway, such as CDK4, CDKN1B and CCND1.

Pathway enrichment analysis revealed that genes mutated in early-relapsing cases were predominantly associated with the PI3K-Akt signaling pathway, cancer-related microRNAs, and human papillomavirus infection pathways, suggesting these signaling networks' involvement in accelerated disease progression. The PI3K-AKT pathway showed the highest enrichment score, corroborating findings from previous studies of early-relapsing cohorts.[28] The PI3K/AKT signaling axis represents a fundamental intracellular pathway that orchestrates critical cellular processes, including survival, metabolism, proliferation, and growth. Dysregulation of this pathway, particularly through oncogenic mutations in PI3K-related genes such as PIK3CA, can lead to constitutive pathway activation and subsequent tumor development and progression. These activating mutations trigger downstream signaling cascades, resulting in uncontrolled protein function and pathway hyperactivation. PIK3CA mutations correlate with increased tumor size and inferior survival outcomes. Furthermore, in hormone receptor-positive (HR+) and HER2-positive breast cancers, these mutations are associated with shortened duration of response to targeted therapies. The study's focus on actionable genetic alterations, such as the PI3K-AKT signaling pathway, opens avenues for targeted therapy development.

Tumor genomic profiling can inform clinical trial enrollment and guide personalized therapeutic strategies. However, the translation of comprehensive genomic analysis into clinical practice faces several challenges. These include the limited availability of targeted therapeutics, complexity in interpreting genomic alterations (particularly distinguishing driver from passenger mutations), and the need for standardized guidelines in prioritizing actionable findings. Furthermore, tumor evolution presents a significant clinical challenge: archived primary tumor tissue may not accurately represent the genomic landscape of advanced disease, and sequential tissue sampling for longitudinal molecular monitoring poses practical limitations in clinical settings.

There were several limitations, including the relatively small cohort size for genetic analysis and the retrospective nature of the data, which might introduce selection bias. Future research should address these challenges to enhance the robustness of the findings. This study primarily focused on analyzing patients with early recurrence, conducting pathological and molecular analyses, and discovered that certain genes showed a degree of clustering in this patient group. Although some other studies have provided evidence, due to the lack of basic research validation in this study, it is not possible to determine whether these altered genes and signaling pathways could serve as therapeutic targets. This requires further research and analysis.

Conclusion

In conclusion, our retrospective analysis has unveiled distinct molecular signatures in early-recurrent breast cancer, characterized by prevalent TP53 and PIK3CA mutations and heightened PI3K-AKT pathway activation. These molecular alterations not only contribute to aggressive disease biology and diminished treatment response but also present possible therapeutic targets. The FDA approval of PI3K-AKT pathway inhibitors, such as Alpelisib and Everolimus, represents significant progress in targeted therapy development. Integration of molecular profiling into clinical practice may enable early identification of high-risk patients and guide personalized treatment strategies. While our findings provide valuable insights into the biological underpinnings of early-relapsed breast cancer, future large-scale validation studies and mechanistic investigations are essential to optimize therapeutic approaches and improve patient outcomes.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request. Raw sequencing data have been deposited in the Genome Sequence Archive (GSA) for Human with the accession code BioProject: HRA006981.

Consent to Participate

This is a retrospective analysis which is designed not to interfere with patients' medical decisions. And a significant number of patients will not be admitted to the hospital anymore, thereby making it extremely challenging to secure written informed consent. In the context of retrospective studies, the strategy of attaining consent from patients and their families through telephone informed consent is a viable option. So we have chosen to adopt this particular approach. The study was approved by the Institutional Review Board of the Nanjing Drum Tower Hospital to be exempted from informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no financial or non-financial competing interests.

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