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RESEARCH ARTICLE

Molecular Subtypes of Breast Cancer in Arab Women: Distribution and Prognostic Insights

Naser Elkum[1] · Abdelilah Aboussekhra[2] · Mouad Aboussekhra[1] · Hanin Aldalham[1] · Lama Alshehri[1] · Saleh Alessy[1] · Taher AL-Tweigeri[3] · Ali Saeed Al-Zahrani[1]

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Abstract

Background Understanding the ethnic molecular subtype characteristics of breast cancer (BC) in Saudi women is crucial for providing comprehensive prognostic information and optimizing patient outcomes, making it essential to study their distribution and impact on survival.

Methods This hospital-based cohort study analyzed clinic–pathological data from 1,035 Saudi women diagnosed with invasive BC and followed for 12 years, at King Faisal Specialist Hospital & Research Center. Cancers were classified into four molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and triple-negative. Survival outcomes were assessed using Kaplan–Meier survival curves and Cox proportional hazard models.

Results Luminal A was the most common molecular subtype (41.7%), followed by luminal B (23.4%), triple-negative (19.5%), and HER2-enriched (15.4%). Age at diagnosis, menopause, and tumor grade were significantly associated with subtypes ($p<0.05$). Survival outcomes varied significantly ($p=0.0202$), with luminal A and B showing the highest 5-year survival rates (~83%), triple-negative at 76.4% (hazard ratio: 1.55), and HER2-enriched tumors had the lowest at 69.1%, with a 1.75-fold higher risk of death. Advanced-stage cancers (III and IV) were strongly associated with increased mortality, with hazard ratios of 2.5 and 7.6, respectively, compared to early-stage disease.

Conclusions Molecular subtypes and stage at diagnosis are key predictors of mortality in Saudi women with BC. The poor outcomes for HER2-enriched and TNBC subtypes highlight the need for timely diagnosis and targeted treatments, emphasizing the importance of personalized care and addressing ethnic variations in BC diagnosis.

Keywords Breast cancer · Molecular subtypes · Breast cancer survival · Histopathological stage · Cancer epidemiology · Arab women

✉ Naser Elkum
nelkum@kfshrc.edu.sa

Abdelilah Aboussekhra
aboussekhra@kfshrc.edu.sa

Mouad Aboussekhra
maboussekhra@gmail.com

Hanin Aldalham
haldalham@kfshrc.edu.sa

Lama Alshehri
lmalshehri@kfshrc.edu.sa

Saleh Alessy
salessy@kfshrc.edu.sa

Taher AL-Tweigeri
ttwegieri@kfshrc.edu.sa

Ali Saeed Al-Zahrani
alisaz@kfshrc.edu.sa

[1] Research and Innovation, GCC Cancer Control and Prevention, King Faisal Specialist Hospital and Research Center, PO BOX 3354, Riyadh, KSA 11211, Saudi Arabia

[2] Cancer Biology and Experimental Therapeutics Section, Department of Molecular Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, KSA, Saudi Arabia

[3] Breast Cancer, Medical Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, KSA, Saudi Arabia

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1 Introduction

Breast cancer (BC) is the most common malignancy and a leading cause of cancer-related deaths among women globally [1]. In the Kingdom of Saudi Arabia (KSA), BC is the most prevalent cancer among females [2], with incidence rates on the rise in line with global trends. The annual age-standardized rate of BC in KSA is 28.4 per 100,000 women, indicating a growing burden of the disease. Currently, BC accounts for 31.4% of all diagnosed cancer cases in KSA [3], highlighting the urgent need for effective screening, early detection, and comprehensive treatment programs to address the impact of BC on the female population.

In Saudi Arabia, an opportunistic breast cancer screening program has been established in 2007 in Riyadh then expanded to other major cities, primarily targeting women aged 40 and above [4]. The program encourages mammography as the primary screening modality and is implemented through governmental and private hospitals, as well as some non-governmental organizations. Additionally, breast self-examination (BSE) and clinical breast examination (CBE) are promoted as awareness and early detection strategies, although they are not formally mandated as part of the national screening protocol. Various public health campaigns also emphasize the importance of early detection through self-awareness initiatives [5].

BC in Arab women is characterized by its high aggressiveness, poor clinicopathological features, and early onset [6]. The disease typically presents in younger women, with a median age of 47 years at diagnosis, which is significantly lower than the median age of 63 years in industrialized nations. This early onset is concerning as it often leads to more advanced stages of the disease at diagnosis, complicating treatment and reducing survival rates [6, 7]. Several studies have shown that a younger age at diagnosis of BC is associated with a poorer prognosis compared to an older age at diagnosis [8]. This is attributed to the biological characteristics of tumors in younger women, which are more aggressive and less responsive to conventional treatments. Our previous research in Saudi women has revealed that a young age at diagnosis (under 40 years) is an independent prognostic factor for disease-free survival [7]. This indicates that regardless of other clinical factors, a younger age at diagnosis can independently predict a shorter disease-free survival.

The substantial heterogeneity of BC poses challenges in accurately assessing tumor aggressiveness, leading to suboptimal treatment decisions and impacting clinical outcomes negatively [9]. Various clinical and histopathological prognostic factors have been investigated to address this complexity [10]. The well-established and widely used prognostic factors are the immunohistochemically determined expression levels of progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) [11]. Molecular typing based on these expression profiles has identified distinct BC subtypes, such as luminal A, luminal B, HER-2-enriched, and triple-negative BC (TNBC), each with varying prevalence across different populations (St Gallen) [12]. These subtypes exhibit unique characteristics related to prognosis, treatment response, and survival [13, 14]. TNBC, affecting 15–20% of patients with BC, is particularly concerning due to its association with the poorest prognosis and survival rates [15, 16]. This subtype lacks ER, PR, and HER-2 expression, making it challenging to treat without targeted therapies.

Currently, data on the molecular subtypes of BC in Saudi women are accessible at treatment centers and used for guiding patient therapies, but they have not been extensively published [17]. Therefore, a better understanding of ethnic-specific molecular characteristics is essential for improving the prognosis and guiding the treatment of patients with BC. To address this knowledge gap, we aimed to ascertain the prevalence and distribution of various breast cancer molecular subtypes among Saudi women. In addition, we investigated the associations between these subtypes and tumor pathological characteristics, as well as their impact on patient survival.

2 Methods

The cohort comprised female patients with histologically confirmed primary BC who were treated at the King Abdullah Oncology Center, King Faisal Specialist Hospital & Research Center (KFSH&RC) in Riyadh. The study included patients diagnosed between June 1999 and August 2007, initially identifying 1,234 patients from the database. However, 199 patients were excluded due to the missing medical records or ER/PR/HER2 data. This research was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Research Ethics Committee (Office of Research Affairs) at KFSH&RC (RAC#2031091).

Patient records were reviewed to collect data on age at diagnosis, histological grade (Scarff-Bloom-Richardson classification), American Joint Committee on Cancer stage (I, II, III, IV), ER and PR status, tumor size, and treatment received. BC cases were categorized into four molecular subtypes based on hormone receptor and HER2 status: luminal A (ER + and/or PR+, HER2–), luminal B (ER + and/or PR+, HER2+), HER2-enriched (ER- and PR–, HER2+), and TNBC (ER– and PR–, HER2–). Additionally, patients were interviewed to gather detailed information on demographic

factors, menstrual and reproductive history, hormone use, and family history of BC.

To compare means and proportions across multiple groups, we conducted a comprehensive analysis of demographic and clinicopathological characteristics among various BC subtypes. Continuous variables were analyzed using one-way analysis of variance, while categorical variables were assessed using the chi-square test. Survival rate disparities among BC subtypes were assessed using the log-rank test. To investigate the association between molecular subtypes and overall survival rates, we employed univariate and multivariable Cox proportional hazard regression models. These models allowed for the simultaneous adjustment of multiple covariates, providing a more precise estimation of the impact of molecular subtypes on survival outcomes. The adjusted covariates included age at diagnosis, body mass index (BMI), menopausal status, tumor stage, and tumor grade. Hazard ratios (HRs) and 95% confidence intervals were calculated to quantify the associations. All statistical analyses were conducted using SAS software, with significance levels set at $p<0.05$ for two-sided tests.

Table 1 Characteristics of the study population

Variables	Categories	Total	%
Age	≤40 years	319	31.1
	>40 years	709	68.9
BMI (kg/m^2)	Lean	169	17.3
	Overweight	308	31.6
	Obese	499	51.1
Menopausal status	Pre-Menopause	556	54.0
	Post-Menopause	474	46.0
Mean age at menopause, years (±SD)		48.2±6.19	
Grade	I	30	3.0
	II	540	53.9
	III	432	43.1
Stage	I	52	5.0
	II	458	44.4
	III	377	36.6
	IV	144	14.0
Surgery type	Lumpectomy	92	11.0
	Lumpectomy + mastectomy	119	14.3
	Mastectomy	452	54.3
	None	170	20.4
Molecular subtypes	Luminal A	432	41.7
	Luminal B	242	23.4
	HER2-enriched	159	15.4
	Triple-negative	202	19.5

BMI, body mass index

Lean: BMI≥18.5 and <25; overweight: BMI≥25 and <30; obese: BMI≥30

3 Results

The clinicopathological characteristics of the patients are summarized in Table 1. A total of 1,035 cases of BC were analyzed, with patients' ages at diagnosis ranging from 19 to 91 years (median: 44.5 years) and 31% below 40 years. The patient demographics included 44.1% illiterate, 25% employed, 94.4% married, 54.0% premenopausal, and 51.1% obese.

Invasive ductal carcinoma (98.0%) was the predominant histological type of BC, with the majority of tumors being moderately differentiated (Grade II) or poorly differentiated (Grade III), representing 53.6% and 43.5% of cases, respectively. Most cases were diagnosed at TNM stages II-III (81.0%), with tumor size exceeding 2 cm in 23% of cases and a median size of 3.25 cm. The most prevalent molecular subtype was luminal A (41.7%), followed by luminal B (23.4%), TNBC (19.5%), and HER2-enriched (15.4%).

Table 2 presents the clinicopathological parameters of patients by molecular subtype. Significant differences were observed between molecular subtypes and age at diagnosis ($p=0.0067$), age at menopause ($p=0.0316$), and tumor grade ($p<0.0001$). TNBC was more common in younger women (25.0% versus 17.3%), with 56.4% of TNBC cases being grade III tumors.

The median survival rate was 11.2 years (interquartile range, 6.4–11.9 years). At the end of the 12-year follow-up period, 77.3% of patients were still alive. Survival rates varied by breast cancer subtype, with 79.9% of luminal A patients, 76.5% of luminal B patients, 76.2% of TNBC patients, and 69.8% of HER2-enriched patients remaining alive at the end of the follow-up period. Univariate analysis (Fig. 1) revealed significant differences in survival between the molecular subtypes ($p=0.0202$). The luminal subtypes had the longest survival, with a 5-year survival reaching 83.4%. The lowest survival was observed in the TNBC and HER2-enriched subtypes, with 5-year survival rates around 76.4% and 69.1%, respectively.

While molecular subtypes influenced BC survival outcomes, the stage at diagnosis emerged as the most decisive factor (Fig. 2). For instance, the survival rates for the HER2-enriched and TNBC were 96% and 95% among patients diagnosed at Stage I, respectively, but it declined sharply to 36% and 24% in those diagnosed with Stage IV. The survival rates for the luminal A and luminal B subtypes were comparable at stages I, II, and III. However, at Stage IV, patients with luminal B showed significantly higher survival rates than those with luminal A.

The Cox regression analysis, adjusted for patient age, BMI, menopausal status, and stage, revealed significant differences in BC survival among various molecular subtypes. Patients with the HER2-enriched subtype had significantly

Table 2 Clinicopathological characteristics by molecular subtypes

Characteristics	Luminal A $n=432$	Luminal B $n=242$	HER2 $n=159$	TNBC $n=202$	*P*-value
Mean age at diagnosis (±SD), **years**	46.8 ± 11.03	44.8 ± 11.19	46.7 ± 10.05	44.1 ± 11.34	**0.0142**
Age					
≤40 years	115 (26.7)	84 (34.7)	43 (27.0)	78 (38.8)	**0.0067**
>40 years	316 (73.3)	158 (65.3)	116 (73.0)	123 (61.2)	
BMI (kg/m^2)					
Lean	70 (17.4)	41 (18.1)	21 (13.9)	34 (17.7)	0.3745
Overweight	123 (30.6)	81 (35.8)	52 (34.4)	51 (26.6)	
Obese	209 (52.0)	104 (46.1)	78 (51.7)	107 (55.7)	
Menopausal status					
Pre	221 (51.8)	136 (56.9)	79 (50.0)	117 (58.2)	0.2482
Post	206 (48.2)	103 (43.1)	79 (50.0)	84 (41.8)	
Mean age at menopause, years (±SD)	49.07 ± 5.53	47.43 ± 6.17	48.23 ± 6.45	46.95 ± 7.18	**0.0316**
Tumor size, cm (±SD)	4.19 ± 3.18	3.77 ± 2.30	4.86 ± 3.86	3.74 ± 2.18	0.2229
Grade					
I	22 (5.3)	5 (2.1)	2 (1.3)	1 (0.5)	**<0.0001**
II	254 (60.8)	145 (61.7)	59 (37.8)	82 (42.5)	
III	142 (34.9)	85 (36.2)	95 (60.9)	110 (57.0)	
TNM stage					
I	27 (6.3)	9 (3.7)	6 (3.8)	10 (4.9)	0.3189
II	191 (44.8)	102 (42.3)	65 (41.1)	99 (49.3)	
III	143 (33.6)	93 (38.6)	65 (41.2)	73 (36.3)	
IV	65 (15.3)	37 (15.4)	22 (13.9)	19 (9.5)	
Surgery type					
Lumpectomy	41 (11.7)	25 (13.0)	8 (6.2)	18 (11.2)	0.0692
Lumpectomy + mastectomy	55 (15.6)	32 (16.7)	11 (8.6)	21 (13.0)	
Mastectomy	186 (52.8)	94 (48.9)	88 (68.8)	84 (52.2)	
None	70 (19.9)	41 (21.4)	21 (16.4)	38 (23.6)	
Radiation therapy					
Yes	227 (59.0)	143 (68.4)	73 (54.5)	107 (61.1)	0.0502
No	157 (41.0)	66 (31.6)	61 (45.5)	68 (38.9)	
Chemotherapy					
Yes	310 (80.7)	164 (78.5)	111 (83.5)	133 (76.3)	0.4304
No	74 (19.3)	45 (21.5)	22 (16.5)	41 (23.7)	
Hormonal therapy					
Yes	224 (58.3)	117 (56.0)	76 (57.1)*	89 (51.2)*	0.5005
No	160 (41.7)	93 (44.0)	57 (42.9)	84 (48.8)	

*These patients were referred from other hospitals, where treatment was initiated before molecular subtyping was performed. Upon reevaluation at KFSH&RC, hormonal therapy was discontinued, and treatment plans were adjusted to align with confirmed receptor status

BMI, body mass index; Lean: BMI ≥ 18.5 and < 25; overweight: BMI ≥ 25 and < 30; obese: BMI ≥ 30

worse survival outcomes compared to those with the luminal A subtype ($p=0.0043$, Table 3). Specifically, the HR for death in patients with the HER2-enriched subtype was 1.75 times higher than that in those with the luminal A subtype. Similarly, patients with TNBC exhibited a higher HR for death at 1.55 compared to those with the luminal A subtype. In contrast, no significant difference in survival was observed between patients with the luminal A and luminal B subtypes.

4 Discussion

4.1 Distribution of Breast Cancer Molecular Subtypes in Saudi Women

This study on the prevalence of breast cancer among Saudi females has revealed consistent molecular subtype patterns compared to global reports, with only minor variations. Indeed, luminal A was the most prevalent subtype (41.7%), followed by luminal B (23.4%) and TNBC (19.5%), while HER2-enriched BC was the least common (15.4%).

The prevalence of TNBC among Saudi women aligns with findings from South Africa, the United States of America (USA Africans), Tunisia, Algeria, and Brazil (18–22.5%)

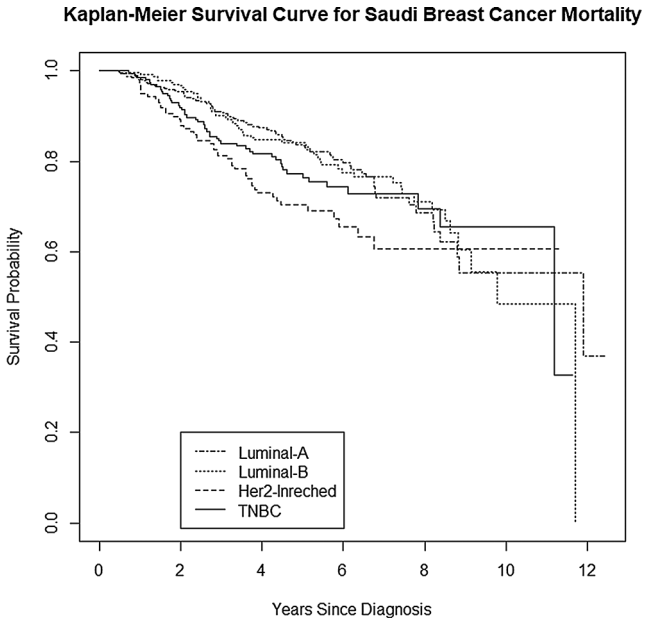

Fig. 1 Survival rates according to molecular subtypes

[14, 15, 18, 19], but is higher than that in Morocco, China, Norway, Canada, the Netherlands, Italy, Spain, Germany, Japan, the Philippines, Korea, and Vietnam (7–14.2%) [20–29]; and lower than that reported in Tanzania, Mali, and Ghana (26–49.4%) [30–33]. Our findings revealed a higher prevalence of the HER2-positive subtype is higher in the Saudi population than in most populations (4–13.7%) [20–24, 27, 34–38] but lower than in Vietnam, Mali, Tanzania, and Ghana [29–31, 33]. The prevalence of luminal A in our study is lower than that reported in Germany, China, South Africa, the Netherlands, Canada, Morocco, the USA, and Turkey (44.7–69%) [20–24, 34, 35, 37, 38], but higher than that reported in Brazil, Vietnam, and Korea [29, 36, 39]. The luminal B subtype accounted for 23.2% of Saudi BC cases, a prevalence higher than previously reported in Morocco [20], South Africa [40], and Asia [29, 38] (19.4%), but lower than in Europe [23, 41].

4.2 Association of Clinicopathological Features with Molecular Subtypes

We identified a strong association between BC molecular subtypes and age at diagnosis. Indeed, TNBC was consistently associated with a younger age at diagnosis compared to other subtypes, consistent with previous findings across diverse populations [20, 23, 39, 42, 43].

Furthermore, there was a significant variation in menopausal age across different molecular subtypes of BC. TNBC was found to be associated with early menopause, while the luminal A subtype was associated with later menopause [41], highlighting the distinct biological and clinical characteristics of various BC subtypes. Early menopause, which results in a rapid decline in estrogen levels, may heighten the risk of aggressive, hormone receptor-negative subtypes like TNBC, possibly due to genetic predispositions like *BRCA1* mutations commonly associated with TNBC. Conversely, the reduced estrogen exposure in early menopause could limit the development of hormone receptor-positive tumors. In contrast, late menopause extends the exposure to estrogen, which may promote the development of luminal A subtypes characterized by high hormone receptor expression. These findings are consistent with previous research findings linking extended estrogen exposure to luminal A subtypes and reveal a novel association between early menopause and TNBC. This underscores the importance of tailored screening strategies based on the menopausal age. Further studies should delve into the genetic and environmental factors contributing to these observed associations.

A subset of HER2-positive and TNBC patients in our cohort initially received hormonal therapy, as treatment was initiated at referring hospitals before comprehensive molecular subtyping. As a national referral center, KFSH&RC receives patients from across the country, many of whom undergo reassessment upon transfer. During the study period 1999–2007, routine IHC subtyping was not universally implemented at all institutions, leading to treatment decisions based on incomplete receptor profiling. Upon reevaluation at our hospital, hormonal therapy was discontinued, and treatment plans were adjusted to align with confirmed receptor status. This highlights the evolving standardization of breast cancer subtyping and the critical role of referral centers in ensuring accurate diagnosis and optimal treatment.

While tumor size did not show a significant correlation with molecular subtypes, consistent with previous study findings [20, 40, 44], we observed a notable association between tumor grade and molecular subtypes ($p<0.0001$). Specifically, higher-grade tumors were more prevalent in the TNBC and HER2 subtypes. This aligns with previous research highlighting the aggressive nature of HER2-positive and TNBC subtypes, which are known for their higher invasiveness and tumor grade [18, 29].

4.3 Prognosis

The analysis highlights the diversity of female BC subtypes in KSA, revealing variations in survival rates based on molecular characteristics. The predominance of the luminal A subtype, associated with better survival rates, contrasts with the significant prevalence of TNBC and HER2-enriched subtypes linked to poorer outcomes, aligning with previous reports [23, 45, 46]. Multivariable Cox regression

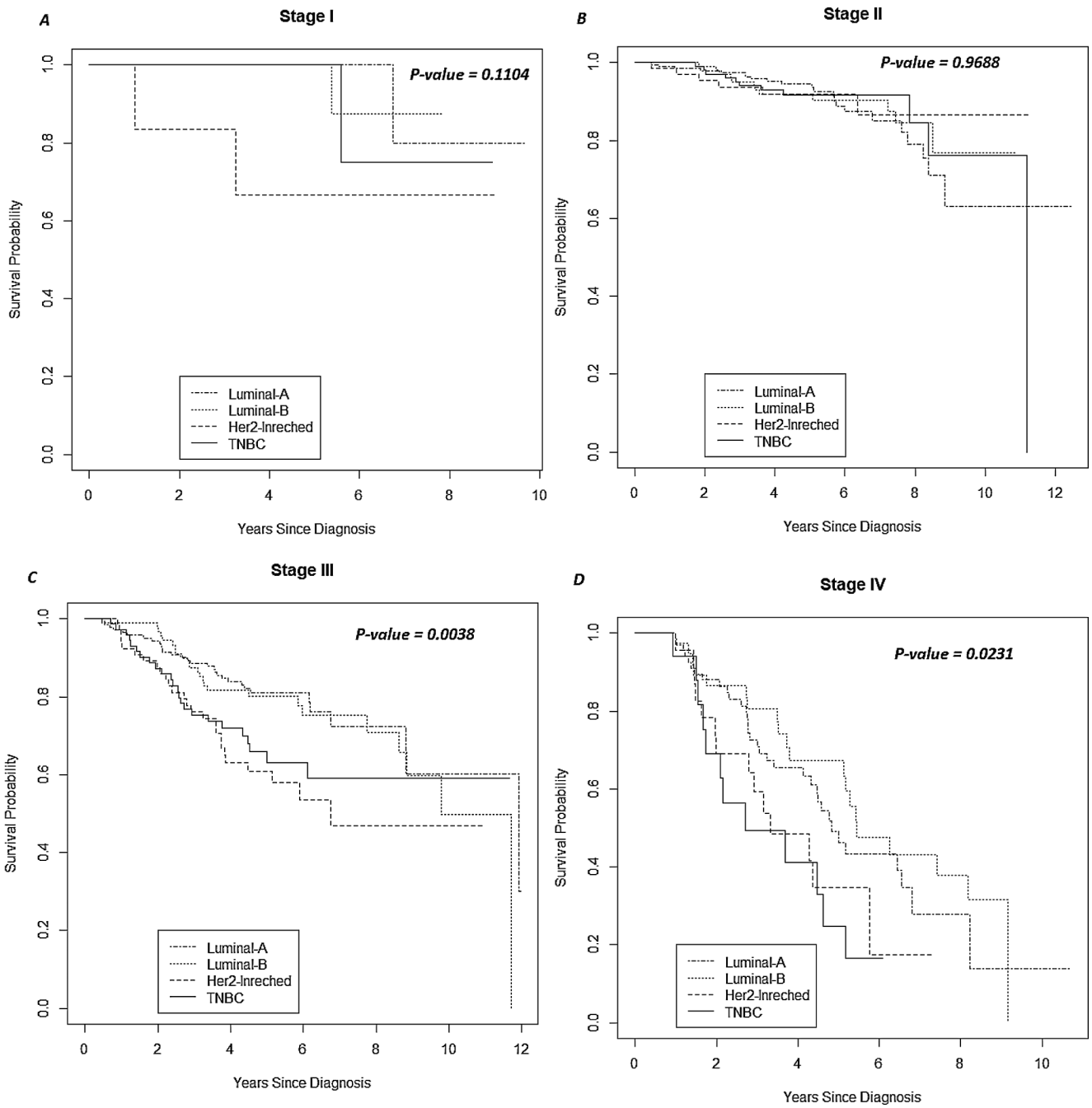

Fig. 2 Breast cancer survival by stage and molecular subtypes among (**A**) Stage I, (**B**) Stage II, (**C**) Stage III, and (**D**) Stage IV

analysis confirmed that BC molecular subtypes are independent prognostic factors for patient survival among Saudi women ($p = 0.0043$). Compared to patients with the luminal A subtype, those with HER2-enriched and TNBC subtypes exhibited worse survival rates (HR: 1.75 and 1.55, respectively), emphasizing the need for targeted therapies for these subtypes.

Stage at diagnosis is crucial in predicting survival outcomes for patients with BC, with Stage IV disease posing the highest risk of death compared to earlier stages. This risk amplification is further influenced by the molecular subtype, with variations in the degree of increase observed across different subtypes. While survival rates for Luminal A and Luminal B subtypes were similar at early stages, a notable divergence appeared at Stage IV, where Luminal B demonstrated a significantly higher survival advantage over Luminal A. Although this finding is consistent with previous studies [14, 47], it is important to contextualize these results within our study setting. In those studies, trastuzumab was available and likely contributed to the improved survival in

Table 3 Risk of death from breast cancer

Variables	Cases	Deaths (%)	Univariate HR	Adjusted HR	95% CI	*P*-value
Molecular Subtypes						
Luminal A	432	87 (21.2)	1	1	-	-
Luminal B	242	57 (23.6)	1.07	0.972	0.682–1.386	0.8755
HER2-enriched	159	48 (30.2)	**1.71**	**1.75**	1.191–2.565	**0.0043**
Triple-negative	202	48 (23.8)	1.25	**1.55**	1.061–2.275	**0.0237**
TNM Stage						
I	52	5 (9.6)	1	1	-	-
II	458	51 (11.1)	1.17	0.974	0.388–2.446	0.9554
III	377	104 (27.6)	**3.35**	**2.53**	1.024–6.664	0.0442
IV	144	78 (54.2)	**9.73**	**7.55**	3.021–18.86	<0.0001

HR: hazard ratio; adjusted for age, BMI, menopause status, stage, and grade

Luminal B patients. However, in our study, trastuzumab was not available during the study period, indicating that the survival advantage of Luminal B patients cannot be attributed to HER2-targeted therapy. Instead, this advantage may stem from intrinsic tumor biology, differences in hormone receptor expression, and increased chemosensitivity-factors that could enhance the responsiveness of Luminal B tumors to systemic treatments even in the absence of targeted therapy. Additionally, proliferation markers such as Ki-67, differential endocrine therapy response, and tumor microenvironment variations may have played a role in shaping these survival outcomes. These findings highlight the complexity of molecular subtype-driven prognosis in advanced-stage breast cancer and reinforce the need for tailored therapeutic strategies, particularly for patients diagnosed at later stages where treatment options remain limited.

To the best of our knowledge, this is the first study in KSA to evaluate 10-year survival rates based on BC subtypes. One potential limitation of our study is its retrospective nature, including patients diagnosed between 1999 and 2007, a period when Trastuzumab was not yet utilized for treatment and was not given to all patients in this cohort. Additionally, Ki-67 was not routinely assessed during the study period, limiting its inclusion in molecular subtyping. While Ki-67 is now increasingly used in IHC4 classification, its clinical application remains challenged by variability in measurement techniques, lack of standardization, and inconsistencies in cut-off values. Future studies incorporating standardized Ki-67 assessments will be essential for refining molecular subtyping and assessing its prognostic impact. To address these limitations, further investigations should be conducted considering contemporary BC management strategies, including assessing Ki-67 levels and using targeted treatments.

This study adds to the growing body of evidence supporting the use of molecular profiling in BC management. This underscores the need for tailored approaches that consider the molecular diversity of the disease, contributing to improved patient care and outcomes globally.

5 Conclusion

Our findings emphasize the crucial role of molecular subtypes as independent predictors of mortality among Saudi women with BC, underscoring the significant impact of biological traits and stage at diagnosis on patient outcomes. The poor prognosis associated with HER2-enriched and TNBC subtypes, along with the influence of advanced-stage diagnosis, underscores the critical need for timely detection and the development of targeted, subtype-specific treatments. These insights deepen our understanding of ethnic disparities in BC prognosis, promoting the advancement of personalized and effective cancer care across diverse populations.

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Author Contributions N. E. participated in the conception and overall supervision of the study, managed and analyzed data, and wrote the manuscript. T. T. selected cases, reviewed medical records, and edited the manuscript; M. A., H. A., L. A., and S. A. collected and organized data, and participated in study coordination; A. A. and A. Z. participated in the study conception, data interpretation, and developing and writing of the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval The study conformed to the principles outlined in the Declaration of Helsinki and the approved guidelines. The study was approved by the Ethical Review Committee at the King Faisal Specialist Hospital and Research Center.

Competing Interests The authors declare no competing interests.

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