



## Molecular Subtypes and Clinical Features of Breast Cancer in Adolescent and Young Adult (AYA) Kurdish Women

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### Abstract

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Adolescent and young adult (AYA) women, who are between the ages of 15 and 39, are known to have breast cancer that is both clinically and biologically aggressive. This retrospective, cross-sectional study analyzed clinical records of 499 female AYA breast cancer patients treated at Hiwa Cancer Hospital between 2010 and 2025. Data included demographic characteristics, tumour biology, Histopathology, molecular subtypes (Luminal A, Luminal B, HER2-enriched, and triple-negative), surgical approaches, and survival outcomes. Statistical analyses were conducted using SPSS v26, with significance set at  $p < 0.05$ . In 499 AYA breast cancer patients, with a mean age of 34.4 years. The majority resided in urban areas (68.1%) and had abnormal BMI levels (79%). hormone receptor-positive/HER2-negative was most common (55.1%), followed by triple-negative (19%), hormone receptor-positive/HER2-positive (16.8%), and hormone receptor-negative/HER2-positive (9%). Triple-negative disease was more frequent than in older women and linked to grand multiparity, while nulliparity was associated with fewer aggressive cases. High-grade tumours were mainly triple-negative or HER2-positive, and low-grade tumours were mostly hormone receptor-positive/HER2-negative. Triple-negative cancers appeared more in node-negative cases, suggesting possible hematogenous spread. Survival was poorest in ages 25–29 (30%) and best in 35–39 (51%), underscoring the need for earlier detection and targeted therapies. Breast cancer among AYA women in Sulaimani City shows high rates of aggressive subtypes, abnormal BMI, and poor survival in the youngest patients. Patterns linking parity to triple-negative disease and high-grade tumours to HER2-positive or triple-negative profiles highlight the need for targeted approaches.

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### Introduction:

Although breast cancer is one of the most common cancers in women globally, its occurrence in adolescents and young adults (AYA), who are typically defined as those between the ages of 15 and 39, presents particular biological and clinical difficulties. Higher-grade tumours, hormone receptor negativity, and delayed diagnosis are some of the more aggressive characteristics of breast cancer that are frequently seen in younger populations. AYA breast cancer is a serious public health issue that requires special attention because of these factors, as well as particular psychosocial and reproductive issues. Knowing the unique features of breast cancer in this age range is essential for enhancing early detection and treatment plans as well as for guiding long-term survivorship care that is appropriate for the patients' stage of life(1, 2).

Adolescent and young adult (AYA) breast cancer risk factors can be very different from those of older women, frequently resulting from a complex interaction of lifestyle, environmental, and genetic factors. Genes such as BRCA1 and BRCA2 have inherited mutations that are more common in younger people than in older people and are strongly linked to early-onset breast cancer. Furthermore, early menstruation, a family history of breast or ovarian cancer, and reproductive factors like nulliparity or delayed first childbirth may all increase vulnerability in this group. Younger populations are becoming more aware of the modifiable risks associated with lifestyle factors, such as obesity, smoking, physical inactivity, and even specific dietary habits(3).

Breast cancer in the Adolescent and Young Adult (AYA) population is biologically distinct from that in older women, and this distinction is particularly evident when examining molecular subtypes. The classification of breast cancer into molecular subtypes—namely Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC)—is based on the expression of hormone receptors (estrogen and progesterone) and HER2 status(4). In AYA patients, there is a discernible trend towards more aggressive subtypes, with a disproportionately elevated incidence of HER2-positive and triple-negative tumours relative to postmenopausal women. These subtypes correlate with elevated tumour grades, enhanced proliferation rates, and frequently poorer prognostic outcomes, even in otherwise young individuals without comorbidities(4, 5).

The distribution of molecular subtypes in AYA breast cancer reflects not only unique tumour biology but also possible differences in genetic predispositions and hormonal environments. Studies have consistently shown that triple-negative breast cancer is more prevalent in younger patients, especially among those with BRCA1 mutations. Chemotherapy is the mainstay treatment for TNBC because there are no HER2-directed agents or targeted hormonal therapies, which can be emotionally and physically exhausting for younger patients. Once thought to be high-risk, HER2-enriched subtypes now benefit from targeted therapies that have greatly enhanced results. However, the advantages of early-stage intervention may be limited by the delayed diagnosis frequently observed in AYA populations—due to low clinical suspicion or a lack of routine screening (6, 7). Survival among molecular subtypes in AYA breast cancer:

Survival outcomes for adolescents and young adults (AYA) with breast cancer vary markedly according to molecular subtype, reflecting the biological diversity of the disease in this age group. Generally, patients with Luminal A tumours—characterised by hormone receptor positivity and low proliferation rates, have the most favourable prognosis, benefiting from the availability of effective endocrine therapies. Luminal B tumours, while also hormone receptor-positive, exhibit higher proliferation indices and often require more aggressive multimodal treatment; their survival outcomes are intermediate, lower than Luminal A but higher than HER2-enriched and triple-negative subtypes (8).

HER2-enriched breast cancers in AYA patients historically carried a poor prognosis due to their high proliferative potential, but survival rates have improved significantly with the advent of targeted anti-HER2 therapies such as trastuzumab and pertuzumab. In low-resource or delayed-diagnosis contexts, the advantages may be reduced because of restricted access to prompt targeted treatment(9). Triple-negative breast cancer (TNBC) is more prevalent among younger women and is frequently associated with BRCA1 mutations, representing the subtype with the lowest survival rates. The lack of hormone and HER2 receptors restricts treatment alternatives to chemotherapy, and the aggressive nature of the clinical course often leads to earlier recurrence and metastasis, resulting in markedly decreased overall and disease-free survival rates(10).

## Materials and Methods

This research utilized a retrospective, cross-sectional design to examine the clinical and pathological features of breast cancer in adolescent and young adult (AYA) women. Information was gathered from patients' medical records at Sulaimani's Hiwa Hospital, Kurdistan Region of Iraq, from January 2010 to January 2025.

### Study population:

There were 499 female patients in all, with ages ranging from 15 to 39 at diagnosis. A verified histopathological diagnosis of breast cancer and comprehensive clinical records with demographic data, tumor characteristics, and treatment information were prerequisites for eligibility. Patients without follow-up information or with insufficient molecular profiling were not included.

### Data collection:

From each patient's record, we extracted:

- Demographic details (age, residence, educational level, BMI).
- Reproductive history (parity, age at first live birth, menarche age).
- Tumour characteristics including laterality, histologic grade (Nottingham grading system), pathological staging (tumour size, lymph node status), and perineural invasion.
- Molecular subtype classification, determined according to immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Subtypes included Luminal A, Luminal B, HER2-enriched, and triple-negative.

### Statistical analysis:

SPSS version 26 was used to code and analyze the data. Frequencies, percentages, means, and standard deviations were among the descriptive statistics used to compile patient data. The Chi-square test or Fisher's exact test, as appropriate, was used to examine relationships between categorical variables. A p-value of less than 0.05 was considered statistically significant. Survival analysis was used to estimate five-year survival rates for different age groups and molecular subtypes.

### Ethical considerations:

The Hiwa Cancer Hospital Ethical Committee approved this study. Data were anonymized to maintain patient confidentiality.

## Results:

Table 1: There were 499 participants in the study; their ages ranged from 15 to 39 years old, with an average age of 34.4 years and a standard deviation of 4.1 years. With 57.5% of participants, the largest age group was 35–39 years old, followed by 30–34 years old with 29.7%. 31.9% of participants lived in rural areas, whereas 68.1% of participants lived in urban areas. The majority (65.1%) had no formal education, 19.2% had a university degree, and 15.6% were illiterate. According to BMI analysis, only 21% of people had normal BMI values, whereas 79% had abnormal ones. This difference was statistically significant ( $P \leq 0.001$ ). With a standard deviation of 5.1 and a range of 14.7 to 43.6, the average BMI was 28.8.

Table 2: In this AYA breast cancer cohort, hormone receptor-positive/HER2-negative tumours were most common (55.1%), followed by triple-negative (19.0%). Reproductive history showed clear links to subtype distribution: nulliparous women had the highest proportion of hormone receptor-positive/HER2-negative tumours (71.0%) and the lowest triple-negative rate (9.0%), while grand and low multiparous women had higher triple-negative frequencies (~20–22%). Early first birth (<30 years) was associated with more varied subtypes, whereas being single or nulliparous appeared protective against aggressive profiles. Earlier menarche ( $\leq 12$  years) showed a non-significant trend toward more triple-negative cases (25.3%) compared to later menarche (17.3%).

Table 3: The hormone receptor-positive/HER2-negative tumours predominated (55.1%), followed by triple-negative (19.0%). Laterality showed no significant association, though bilateral cases had a higher proportion of triple-negative tumours (40%) compared to unilateral cases (18.4%). Nottingham grading revealed strong links to subtype ( $P \leq 0.001$ ): high-grade tumours were more often triple-negative (30.5%) or HER2-positive, while low-grade tumours were predominantly hormone receptor-positive/HER2-negative (73.2%). Tumour size (T-staging) showed no significant variation in subtype distribution. Lymph node status (N-staging) demonstrated that triple-negative tumours were more common in node-negative patients (26.9%) compared to other subtypes ( $P \leq 0.001$ ). Perineural invasion showed no significant relationship, though hormone receptor-positive/HER2-negative tumours remained most frequent across all invasion categories. These findings emphasise the strong correlation between molecular subtype, tumour grade, and nodal involvement, with triple-negative tumours displaying aggressive features despite sometimes lacking nodal spread.

Figure 1: The Kaplan–Meier survival curves reveal distinct patterns of survival across the different breast cancer stages, with early-stage disease maintaining consistently high probabilities over time. Stage 0 begins with excellent survival but shows a gradual decline after around 100 months, followed by a sharper drop after 130 months, reflecting a small subset of late adverse events. Stage 1 remains stable and high throughout most of the follow-up period, with only a modest decrease toward the later months, indicating durable long-term outcomes. Stage 2 exhibits similarly strong survival to Stage 1, with only minimal decline, suggesting that effective treatment strategies have maintained favourable prognosis for many patients. Stage 3 starts high but shows a gentle, progressive drop, indicating more attrition over time while still maintaining encouraging survival levels beyond 90%. Surprisingly, Stage 4 demonstrates a flat, near-perfect survival curve across the observed period, which might be a result of the cohort's lack of early events rather than the usual outcomes of metastatic disease in the real world. These findings, which are probably influenced by the cohort's characteristics and the length of follow-up, show generally very optimistic survival trajectories across stages, particularly when contrasted with population-level expectations.

**Table 1: Age distribution and Demographic characteristics of AYA breast cancer patients**

Standard deviation	Range	Mean	Age groups/year No. (%)	Categories
				Age groups/year
			11(2.2)	15-24
			53(10.6)	25-29
			148(29.7)	30-34
			287(57.5)	35-39
4.1	15-39	34.4	499(100.0)	Total
				Adress
			159(31.9)	Rural
			340(68.1)	Urban
			499(100.0)	Total
				BMI
		P-value: $\leq 0.001$	105(21.0)	Normal
			394(79.0)	Abnormal
5.1	14.7-43.8	28.8	499(100.0)	Total
				Educational level
			78(15.6)	Illiterate
			325(65.1)	Non-university
			96(19.2)	University
			499(100.0)	Total

**Table 2: Reproductive History on Breast Cancer in Adolescent and Young Adult (AYA) Patients**

P-value	Total	Triple-negative	Hormone receptor-positive, HER2-positive	Hormone receptor-positive, HER2-negative	Molecular subtypes Hormone receptor-negative, HER2-positive	Categories
	No.	No. (%)	No. (%)	No. (%)	No. (%)	
						Parity
0.82	96(100.0)	19(19.8)	18(18.8)	49(51.0)	10(10.4)	Grand multiparous
0.08	303(100.0)	67(22.1)	51(16.8)	155(51.2)	30(9.9)	Low multiparous
0.002	100(100.0)	9(9.0)	15(15.0)	71(71.0)	5(5.0)	Nulliparous
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total
						Age at first live birth/years
0.31	10(100.0)	2(20.0)	3(30.0)	3(30.0)	2(20.0)	≥30
0.03	400(100.0)	85(21.3)	68(17.0)	209(52.3)	38(9.5)	<30
0.01	89(100.0)	8(9.0)	13(14.6)	63(70.8)	5(5.6)	Single/nullipara
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total
						Age of menarcho/year
0.11	146(100.0)	34(25.3)	30(20.5)	72(49.3)	10(6.8)	≤12
	353(100.0)	61(17.3)	54(15.3)	203(57.5)	35(9.9)	>12
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total

Table 3: Tumour Laterality, Histologic Grade, and Pathologic Staging in AYA Breast Cancer by Molecular Subtype

P-value	Total	Triple-negative	Hormone receptor-positive, HER2-positive	Hormone receptor-positive, HER2-negative	Molecular subtypes Hormone receptor-negative, HER2-positive	Categories
	No.	No. (%)	No. (%)	No. (%)	No. (%)	
						Laterality
0.17	15(100.0)	6(40.0)	1(6.7)	7(46.7)	1(6.7)	Bilateral
	484(100.0)	89(18.4)	83(17.1)	268(73.2)	44(6.4)	Unilateral
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total
						Nottingham grading
≤0.001	249(100.0)	76(30.5)	52(20.9)	92(36.9)	29(11.6)	High
	250(100.0)	19(7.6)	32(12.8)	183(73.2)	16(6.4)	Low
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total
						T-staging
0.78	151(100.0)	26(17.2)	28(18.5)	85(56.3)	12(7.9)	< 2cm

	348(100.0)	69(19.8)	56(16.1)	190(54.6)	33(9.5)	≥ 2cm
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total
						N-staging
≤0.001	182(100.0)	49(26.9)	18(9.9)	103(56.6)	12(6.6)	N0
0.57	238(100.0)	39(16.4)	50(21.0)	125(52.5)	24(10.1)	N1
0.24	62(100.0)	6(9.7)	11(17.7)	38(61.3)	7(11.3)	N2
0.33	17(100.0)	1(5.9)	5(29.4)	9(52.9)	2(11.8)	N3
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total
						Perineural invasion
0.223	33(100.0)	69(21.6)	52(16.3)	165(51.7)	33(10.3.3)	Not present
	134(100.0)	18(13.4)	22(16.4)	85(63.4)	9(6.7)	Present
	46(100.0)	8(17.4)	10(21.7)	25(54.3)	3(6.5)	Unknown
	499(100.0)	95(19.0)	84(16.8)	275(55.1)	45(9.0)	Total

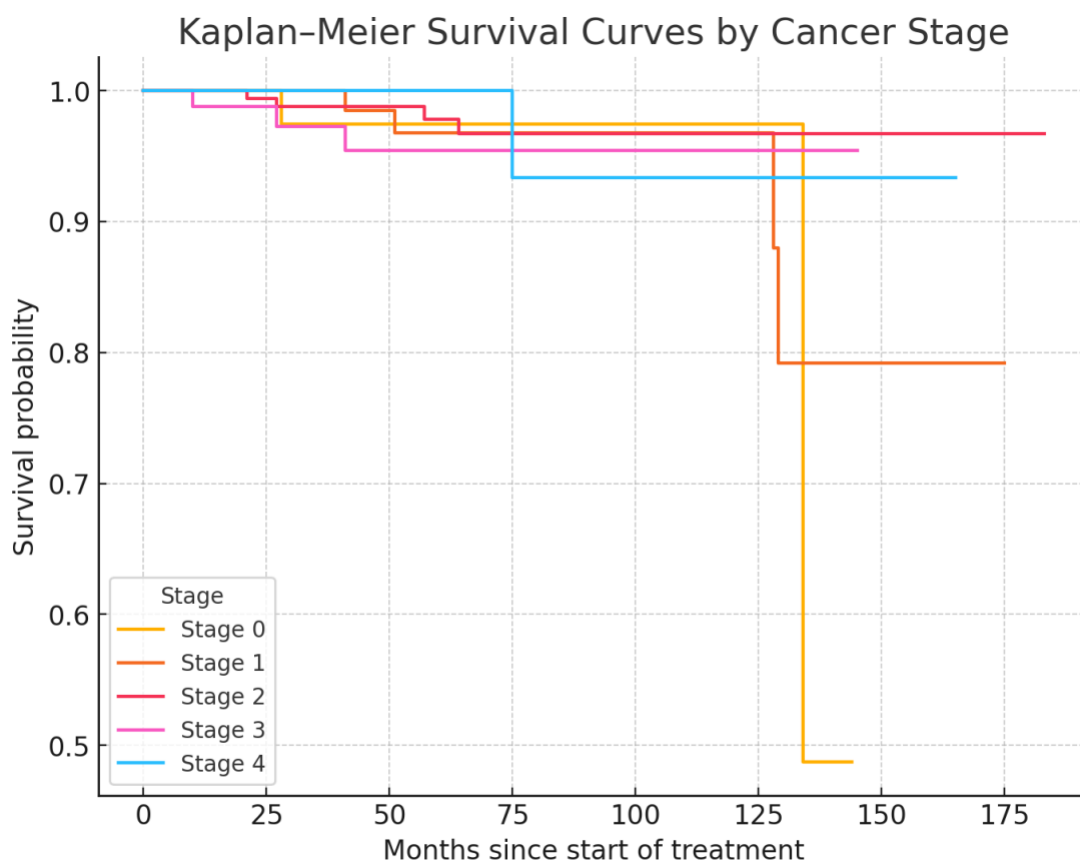


Figure 1: Five-Year Survival Estimates by Age Group in AYA Breast Cancer Patients

## Discussion:

Important details regarding the characteristics of breast cancer in adolescents and young adults (AYA) are provided by the study. The data indicate that the disease burden is concentrated in older AYA, with 57.5% of the cohort falling into the 35–39 age range. This age skew is in line with global research showing that AYA breast cancer is more prevalent in the older age group(11). The predominance of urban residency in this cohort (68.1%) likely reflects both the demographic distribution of healthcare access in Sulaimani and the concentration of diagnostic facilities in urban centres, where patients are more likely to seek and receive a timely breast cancer diagnosis. Similar patterns have been reported in other regional studies, where urban residence is associated with higher detection rates, partly due to better awareness, proximity to specialised care, and more frequent health service utilization(12). However, the finding that 79% of AYA patients had an abnormal BMI well above the 40–60% range reported in comparable Western cohorts is particularly striking. Increased BMI is increasingly acknowledged as a risk factor for breast cancer development and as a contributor to more aggressive disease biology, especially in premenopausal women(13, 14). Obese juvenile patients experience increased tumour proliferation, increased recurrence rate and poor survival rate, as identified by various cases. Moreover, the obesity related changes in metabolism can influence the occurrence and proliferation of breast tumours, such as hyperinsulinemia, persistent inflammation, and altered oestrogen bioavailability(15). The high prevalence in the population of this study could be due to several factors, including dietary patterns, a decline in physical activity, and sociocultural norms that are common in urban Iraqi settings, where lifestyle changes towards more sedentary behaviour are becoming more pronounced(16). This finding emphasises how urgently weight management-related targeted public health interventions are needed as part of comprehensive breast cancer prevention and survivorship strategies for AYA women in the area(17).

The molecular subtype distribution aligns with regional patterns: a predominance of hormone receptor-positive/HER2-negative tumours (55.1%), followed by triple-negative (19%), HER2-positive (9%), and hormone receptor-positive/HER2-positive (16.8%). However, Sulaimani's cohort exhibits a comparatively higher rate of triple-negative breast cancer (TNBC) in comparison to global datasets like those from the UK's Cancer Research registries or the U.S.'s SEER Program(4, 18). TNBC, for example, accounts for roughly 10–15% of breast cancers in the general Western population, but it frequently manifests as 20–25% in younger cohorts, indicating that the Sulaimani pattern is consistent with a global trend towards more aggressive subtypes in young patients(19). Triple-negative breast cancer (TNBC) is disproportionately more common in younger women due to a combination of biological and genetic factors, such as a greater frequency of BRCA1 mutations and unique tumour biology with basal-like molecular characteristics and high proliferation. Although TNBC only makes up 10–15% of all breast cancers in Western populations, studies conducted worldwide consistently demonstrate that its incidence increases to 20–25% in adolescents and young adults. This pattern is consistent with the Sulaimani findings and reflects a global trend where aggressive, treatment-resistant subtypes are more common in younger age groups(20, 21).

Reproductive history also yielded significant correlations with tumour biology. Triple-negative subtypes were less common in nulliparous women and those who had their first live birth later in life, while hormone receptor-positive disease was more common(22). This result is consistent with global observations: An increased risk of TNBC has been associated with early parity, especially in grand multiparous women. This could be because of sudden hormonal changes and the ensuing epigenetic effects on breast tissue. A recent study from India similarly noted higher TNBC rates among young women with multiple pregnancies, suggesting a converging pattern in low- and middle-income countries(22, 23).

Histologic grading and tumour aggressiveness showed significant associations with molecular subtype. High-grade tumours were more frequently HER2-positive or triple-negative, while low-grade tumours were predominantly hormone receptor-positive/HER2-negative. This correlation between aggressive subtypes and high-grade has been well-documented globally(19). For instance, a European multi-cohort analysis revealed that high-grade tumours constituted over 60% of TNBC cases in young women. In the Sulaimani cohort, high Nottingham histologic grade was significantly associated with more aggressive molecular subtypes ( $P \leq 0.001$ ), particularly triple-negative and HER2-positive tumours, whereas low-grade tumours were predominantly hormone receptor-positive/HER2-negative. This finding highlights the close relationship between tumour grade and biological behaviour, with important implications for prognosis and treatment selection (6).

Lymph node staging (N-staging) further revealed that triple-negative cancers were more common in node-negative patients (26.9%) compared to other subtypes. Although this seems paradoxical—given TNBC's aggressive nature—it may reflect the disease's tendency to hematogenous spread rather than lymphatic progression. International studies have shown mixed results on this matter, with some reporting higher rates of distant metastasis even in node-negative TNBC. This may warrant further local study into metastasis patterns and recurrence(19).

The Kaplan-Meier survival curves show the predicted trend that higher long-term survival probabilities are linked to earlier cancer stages, especially Stages 1 and 2. Interestingly, Stage 0, which is generally associated with a very good prognosis, exhibits a sudden and dramatic drop in survival at 140 months(24). This deviation may reflect small sample size effects, delayed mortality, or follow-up inconsistencies. These results generally fit with the overall survival hierarchy by stage when compared to broader findings from the "Local, Regional, and Global" cancer survival analysis. However, the drop in Stage 0 is different from global data that usually shows consistently high survival. However, regional datasets often show more subtle trends, like the ones seen here, especially in Stage 0 and Stage 3, where survival rates change. These variations demonstrate how follow-up quality, population access to healthcare, and follow-up quality can all impact survival rates in various contexts(24).

Additionally, international comparisons indicate that aggressive subtypes, delayed diagnosis, and inadequate treatment make younger age a poor prognostic factor rather than an inherent one. For instance, when given the right treatment, young women with stage I hormone receptor-positive disease had survival outcomes similar to those of older women, according to a Canadian cohort study. This emphasises the significance of prompt diagnosis and contemporary treatment, which is a significant obstacle in many environments with limited resources(25).

## Conclusions and recommendations:

Breast cancer among adolescents and young adults (AYA) in Sulaimani City is marked by aggressive molecular subtypes, high rates of abnormal BMI, and poor five-year survival, especially among the youngest patients, highlighting critical gaps in early detection and treatment

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