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Stage-Dependent Differences in Quality of Life Among Breast Cancer Patients Prior to Initiation of a Line of Systemic Therapy: A Cross-sectional Study

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Introduction: Disease stage is a key determinant of health-related quality of life (HRQoL) in breast cancer, yet stage-specific HRQoL data prior to systemic therapy remain limited in low- and middle-income countries (LMICs). Understanding baseline HRQoL variation across stages may support more tailored supportive care. This study aimed to evaluate stage-specific differences in baseline HRQoL among women with breast cancer prior to initiation of a line of systemic therapy.

Materials and Methods: In this cross-sectional study at two referral centers in East Java, Indonesia, we consecutively enrolled women with histologically confirmed breast cancer before initiating a new line of systemic therapy. Sociodemographic and tumor characteristics were documented, and HRQoL was assessed using validated Indonesian versions of the EORTC QLQ-C30 and QLQ-BR23. Patients were categorized as having early-stage (n=14), locally advanced (n=62), or metastatic disease (n=30). Group differences were examined using the Kruskal–Wallis test with Bonferroni-adjusted pairwise comparisons.

Results: Invasive ductal carcinoma predominated across stages (80–100%), with higher-grade tumors more frequent in locally advanced disease and Luminal B subtypes more common in advanced stages. Global health status differed significantly by stage (p=0.004), with both early-stage versus metastatic disease (p=0.009) and locally advanced versus metastatic disease (p=0.021) comparisons remaining significant after Bonferroni correction. Social functioning showed stage differences (p=0.022), though pairwise comparisons did not remain significant. Pain demonstrated significant overall variation (p=0.041), with early-stage versus metastatic disease showing a Bonferroni-adjusted difference (p=0.034). Systemic therapy–related side effects differed across stages (p=0.025), but no pairwise comparison met the corrected threshold. Emotional, cognitive, and body-image scores were similar across groups.

Conclusion: Prior to systemic therapy, women with metastatic breast cancer reported significantly lower global health status and higher pain compared with those with early-stage disease, while other differences across stages were more modest after adjusting for multiple comparisons. These findings underscore the value of incorporating baseline HRQoL assessment into oncology evaluation to identify patients with greater supportive-care needs, particularly those presenting with advanced disease.

Introduction

Breast cancer is the most common malignancy among women globally and a leading cause of morbidity and mortality [1]. Disease stage at presentation remains one of the strongest determinants of clinical outcomes and patient experience, particularly in low- and middle-income countries (LMICs) where women frequently present with locally advanced or metastatic disease due to limited screening access, sociocultural barriers, and diagnostic delays [2]. These disparities may influence not only survival but also the health-related quality of life (HRQoL) experienced before systemic therapy is initiated. HRQoL assessment has become an integral component of oncologic evaluation, providing insight into patients' functional status, symptom burden, and psychosocial well-being beyond traditional clinical endpoints [3, 4]. Instruments such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23 allow standardized measurement of multidimensional QoL domains and are widely validated, including in Southeast Asian populations [5]. However, stage-stratified HRQoL data from real-world LMIC settings remain scarce. Existing literature suggests that advanced disease is associated with worse baseline QoL due to higher tumor burden, pain, fatigue, and psychosocial distress, [6-8] yet the extent and specific patterns of these differences in resource-constrained environments are not well defined.

To address this evidence gap, we conducted a cross-sectional study evaluating HRQoL among women with early-stage, locally advanced, and metastatic breast cancer prior to initiation of a line of systemic therapy. The primary aim of this study was to compare HRQoL domain scores across breast cancer stages prior to a line of systemic therapy using validated EORTC instruments, and the secondary aims were to describe demographic and tumor characteristics by stage, and to identify stage-specific symptom patterns.

Materials and Methods

Study design

This was a cross-sectional study conducted at two secondary referral centers in East Java, Indonesia, from January to October 2025, both of which provide comprehensive diagnostic and therapeutic services for breast cancer. The study was designed to evaluate HRQoL across different clinical stages of breast cancer prior to initiation of a line of systemic therapy. Data collection occurred during each patient's pre-treatment evaluation. Ethical approvals were obtained from the institutional review boards of both participating hospitals (197/KEP/2024 from Universitas Airlangga Hospital and 445/02/KOM.ETIK/2025 from Haji General Hospital), and all participants provided written informed consent.

Study population and sample selection

The study consecutively enrolled adult women with histologically confirmed breast cancer who were scheduled to begin a new line of systemic pharmacotherapy, including chemotherapy,

endocrine therapy, or targeted therapy. Patients were recruited consecutively during outpatient oncology evaluations to reflect real-world clinical presentation. In our centers, initiation of systemic pharmacotherapy requires a Karnofsky Performance Status above 70 or an Eastern Cooperative Oncology Group (ECOG) performance status of 1–2; therefore, all patients included in this study met these performance thresholds, even though formal ECOG/Karnofsky scores were not consistently recorded in the medical records. The sample size was calculated using G*Power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Germany) based on prior HRQoL variance estimates from an Asian breast cancer population using the EORTC QLQ-C30 and QLQ-BR23 instruments [5, 9]. We assumed a small-to- moderate effect size of 0.30 for differences in HRQoL domain scores between disease stages, with a two-tailed α of 0.05 and power (1–β) of 0.80. Using these parameters and the standard deviation estimates reported in previous validation studies, the minimum required sample size was 90 participants. Ultimately, 106 patients were included and categorized into early-stage, locally advanced, and metastatic groups according to TNM-based clinical staging.

Inclusion and exclusion criteria

Eligible participants were women aged 18 years or older with histopathologically confirmed breast cancer (Figure 1).

Figure 1. Flowchart of Study Design.

All participants were required to be able to understand and complete the HRQoL questionnaires and have a planned initiation of systemic therapy following baseline assessment. Patients were excluded if they had severe cognitive impairment or psychiatric conditions that could interfere with questionnaire reliability, a concurrent active malignancy, recent systemic treatment within the last 3 months that could affect pre-treatment HRQoL values, or if they were unwilling or unable to provide informed consent. These criteria ensured that the pre-treatment assessments captured the true impact of disease burden rather than residual treatment effects or unrelated clinical factors.

Clinical and histopathologic data collection

Baseline demographic information (age, sex, education level, employment status, marital status) and comorbidity profiles were collected during clinical interviews and chart review. Tumor characteristics including histopathologic subtype, grade, and immunohistochemistry (IHC) profiles (ER, PR, HER2, and Ki67) were extracted from pathology reports. Clinical staging was assigned using the American Joint Committee on Cancer (AJCC) 8th edition TNM system. These data were used to classify patients into early-stage (stage I-IIA), locally advanced (stage IIB-III), or metastatic (stage IV) breast cancer groups, forming the basis of stage-stratified comparisons.

QoL assessment

HRQoL was measured using the validated Indonesian- language versions of the EORTC QLQ-C30 and the breast cancer–specific module EORTC QLQ-BR23. Of note, the Indonesian versions of the QLQ-C30 and QLQ-BR23 have undergone formal validation with acceptable Cronbach’s alpha values reported across major domains, and therefore internal consistency was not re-estimated in this study, which was not designed as a psychometric validation [9, 10]. The QLQ-C30 assesses global health status and functioning (physical, emotional, cognitive, role, social), as well as common cancer-related symptoms (fatigue,pain, nausea/vomiting, dyspnea, insomnia, appetite loss). The QLQ-BR23 captures breast cancer–specific concerns such as body image, sexual functioning,

systemic therapy side effects, breast/arm symptoms, and distress related to hair loss. All scores were linearly transformed to a 0–100 scale according to EORTC scoring guidelines, with higher scores indicating better functioning or greater symptom burden, depending on the scale.

Data management and quality control

Data were collected using standardized forms and entered into a secure, password-protected electronic database. Double-entry verification was performed by independent research assistants to minimize transcription errors. Missing questionnaire items were handled according to EORTC manual protocols, allowing score computation when ≥50% of items within a given domain were completed. Missing data for tumor grade and IHC subtype were coded as “unknown” and reported descriptively. These variables were not incorporated into HRQoL comparisons or multivariable models, as the primary analysis focused on differences across disease stage rather than biomarker-specific subgroups. Because stage-based HRQoL comparisons did not depend on pathology completeness, no sensitivity analyses were performed.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics across disease stages. Continuous variables were presented as means with standard deviations or medians with interquartile ranges, depending on distribution assessed via Shapiro–Wilk testing. Categorical variables were summarized as frequencies and percentages. To examine differences in HRQoL across early, locally advanced, and metastatic breast cancer, the Kruskal–Wallis test followed by Bonferroni-adjusted pairwise comparisons were used for continuous, non- parametric domain scores. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY). Of note, this study was designed as an exploratory stage-stratified HRQoL comparison. Because subgroup sample sizes particularly in the early-stage group were modest, we employed unadjusted non-parametric tests (Kruskal–Wallis) to minimize model overfitting and unstable parameter estimates. Multivariable regression was considered; however, the number of potential confounders relative to events per variable did not allow for adequately powered adjusted models. Therefore, HRQoL comparisons are presented as unadjusted exploratory findings.

Ethical considerations

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was granted by both institutional review boards prior to initiation. Participants received verbal and written explanations about the study purpose, procedures, and confidentiality safeguards, and informed consent was obtained before any data collection.

Results

Baseline characteristics of the study population

A total of 106 women with breast cancer were included in the analysis, comprising 14 patients with early-stage disease, 62 with locally advanced disease, and 30 with metastatic disease (Table 1).

Parameter	Early	Locally advanced	Metastatic

	(N = 14)	(N = 62)	(N = 30)
Sex (n; %)			
Female	14 (100.0)	62 (100.0)	30 (100.0)
Age in years (mean ± SD)	54.79 ± 9.1	51.73 ± 9.9	50.97 ± 9.7
Education (n; %)			
No formal education	0 (0.0)	1 (1.6)	1 (3.3)
Elementary	3 (21.4)	13 (21.0)	6 (20.0)
Secondary	1 (7.1)	3 (4.8)	4 (13.3)
High school	6 (42.9)	17 (27.4)	12 (40.0)
Higher education / university	4 (28.6)	28 (45.2)	7 (23.3)
Employment status (n; %)			
Unemployed	10 (71.4)	38 (61.3)	22 (73.3)
Employed	4 (28.6)	24 (38.7)	8 (26.7)
Marital status (n; %)			
Single	0 (0.0)	4 (6.5)	4 (13.3)
Married	14 (100.0)	51 (82.3)	26 (86.7)
Widow	0 (0.0)	7 (11.3)	0 (0.0)
Comorbidities (n; %)			
No	5 (35.7)	22 (42.9)	16 (53.3)
Yes:	9 (64.3)	40 (57.1)	14 (46.7)
Hypertension (n)	6	22	4
Diabetes mellitus (n)	0	5	7
Cardiovascular diseases (n)	2	8	6
Respiratory diseases (n)	3	3	1
Miscellaneous (n)	5	26	6
History of breast cancer treatment (n; %)			
No	1 (7.1)	24 (38.7)	7 (23.3)
Yes:	13 (92.9)	38 (61.3)	23 (76.7)
Surgery (n)	13	32	15
Pharmacotherapy (n)	6	20	23
Radiotherapy (n)	0	2	2

Table 1. Baseline Characteristics of the Study Population.

All participants across the three groups were female. The mean age differed slightly by stage, with early-stage patients being the oldest group (54.79 ± 9.1 years), followed by those with locally advanced disease (51.73 ± 9.9 years), and those with metastatic disease (50.97 ± 9.7 years). The distribution of educational attainment varied across the three groups. In the early-stage group, most patients had completed high school (42.9%) or higher education (28.6%). In contrast, the locally advanced group had a higher proportion of individuals with university-level education (45.2%), while elementary education accounted for 21.0%. The metastatic group showed a broader distribution, with 40.0% having completed high school, 23.3% having higher education, and 20.0% completing elementary school. Very few patients across all groups had no formal education. Employment patterns were similar across disease stages. In the early-stage group, 71.4% of patients were unemployed, while 28.6% were employed. Locally advanced disease demonstrated a slightly lower proportion of unemployment (61.3%), whereas the metastatic group had the highest proportion of unemployed participants (73.3%). Most patients across all stages were married. All patients with early-stage disease (100%) were married. Among the locally advanced group, 82.3% were married, 6.5% were single, and 11.3% were widowed. In the metastatic group, 86.7% were married and 13.3% were single, with no widowed patients recorded.

The prevalence of comorbidities differed among the groups. Early-stage patients had the highest proportion of comorbidities (64.3%), followed by the locally advanced group (57.1%) and the

metastatic group (46.7%). Hypertension was the most frequently reported comorbidity in all stages, with six cases in early-stage, twenty-two in locally advanced, and four in metastatic disease. Diabetes mellitus was most prevalent among metastatic patients (n = 7), whereas cardiovascular disease was most common in the locally advanced group. Miscellaneous comorbidities including conditions not classified under major organ systems were reported in all groups, with the highest frequency in the locally advanced cohort. Most patients had a history of prior breast cancer-related treatment. Prior therapy was reported in 92.9% of early-stage, 61.3% of locally advanced, and 76.7% of metastatic patients. Surgical history was common, with nearly all early-stage patients (13 out of 14) having undergone surgery, compared with 32 patients in the locally advanced group and 15 in the metastatic group. Prior pharmacotherapy was reported in 6 early-stage, 20 locally advanced, and 23 metastatic patients. Radiotherapy was infrequently reported across all groups, noted in only two patients each in the locally advanced and metastatic categories, and none in the early-stage group.

Breast cancer characteristics

The distribution of tumor histopathology varied across disease stages (Table 2).

Parameter	Early	Locally advanced	Metastatic
	(N = 14)	(N = 62)	(N = 30)
Tissue histopathology (n; %)			
Invasive ductal carcinoma (IDC)	14 (100.0)	51 (82.3)	24 (80.0)
Invasive lobular carcinoma (ILC)	0 (0.0)	4 (6.5)	1 (3.3)
Mixed type of IDC and ILC	0 (0.0)	4 (6.5)	4 (13.3)
Miscellaneous (e.g., mucinous)	0 (0.0)	1 (1.6)	0 (0.0)
Unknown	0 (0.0)	2 (3.2)	1 (3.3)
Tumor grade (n; %)			
Grade I	1 (7.1)	6 (9.7)	3 (10.0)
Grade II	6 (42.9)	19 (30.6)	13 (43.3)
Grade III	6 (42.9)	30 (48.4)	7 (23.3)
Unknown	1 (7.1)	7 (11.3)	7 (23.3)
Immunohistochemistry (n; %)			
Luminal A	3 (21.4)	4 (6.5)	3 (10.0)
Luminal B HER2-	3 (21.4)	17 (27.4)	8 (26.7)
Luminal B HER2+	2 (14.3)	11 (17.7)	7 (23.3)
HER2 enriched	4 (28.6)	11 (17.7)	1 (3.3)
HER2 low	1 (7.1)	3 (4.8)	3 (10.0)
TNBC	1 (7.1)	5 (8.1)	2 (6.7)
Unknown	0 (0.0)	11 (17.7)	6 (20.0)
Metastasis site (n)			
Brain	0	0	1
Lung / Pleura	0	0	16
Liver	0	0	9
Bone	0	0	10

Table 2. Breast Cancer Profile of the Study Population.

All patients with early-stage breast cancer had invasive ductal carcinoma (IDC) (100%), with no cases of invasive lobular carcinoma (ILC), mixed histology, or other subtypes recorded. In the locally advanced group, IDC remained the predominant histologic type (82.3%), followed by ILC

(6.5%), mixed IDC–ILC tumors (6.5%), and a small number of miscellaneous subtypes (1.6%). Two cases (3.2%) had insufficient information and were categorized as unknown. Among patients with metastatic disease, IDC also constituted the majority (80.0%), while ILC and mixed tumors were observed in 3.3% and 13.3% of patients, respectively. One metastatic case (3.3%) was assigned to the miscellaneous category. Tumor grade distributions differed between early, locally advanced, and metastatic disease. Early-stage breast cancer demonstrated a balanced distribution between grade II (42.9%) and grade III tumors (42.9%), with grade I tumors accounting for 7.1% of cases and one case (7.1%) classified as unknown. In the locally advanced cohort, grade III tumors were the most common (48.4%), followed by grade II (30.6%) and grade I (9.7%); seven cases (11.3%) had no available grading information. In patients with metastatic disease, grade II tumors were most frequent (43.3%), followed by grade III (23.3%) and grade I (10.0%). The metastatic cohort also had seven cases (23.3%) categorized as unknown grade, representing the highest proportion of missing grading data among the three groups.

IHC subtypes demonstrated variability across disease stages. Among early-stage patients, Luminal A and Luminal B (HER2–) each accounted for 21.4% of cases. Luminal B (HER2+) and HER2-enriched subtypes constituted 14.3% and 28.6% of cases, respectively. HER2-low and triple-negative breast cancer (TNBC) each represented 7.1% of the early-stage group, with no unknown cases reported. In the locally advanced group, Luminal B (HER2–) was the most common subtype (27.4%), followed by Luminal B (HER2+) and HER2-enriched subtypes, each accounting for 17.7%. Luminal A made up a smaller proportion (6.5%). HER2-low tumors were identified in 4.8% of patients, and TNBC in 8.1%. Eleven patients (17.7%) had incomplete IHC results and were classified as unknown. In the metastatic group, Luminal B (HER2–) remained the most frequent subtype (26.7%), followed by Luminal B (HER2+) (23.3%). Luminal A and HER2-low subtypes each accounted for 10.0% of metastatic cases, whereas HER2-enriched tumors were observed in 3.3% of patients. TNBC was identified in 6.7% of metastatic patients. The metastatic cohort also had a notable proportion of cases (20.0%) with unknown IHC data.

QoL comparison across disease stages

Global health status scores showed variation across disease stages (Table 3).

Parameter	Early	Locally advanced	Metastatic	p-value#
	Median [IQR]	Median [IQR]	Median [IQR]	
	(N = 14)	(N = 62)	(N = 30)	
Global health status				
Quality of life (QL2)	83.3 [81.3 – 93.8]	83.3 [66.7 – 91.7]	75.0 [47.9 – 83.3]	0.004
C30 – Functional scale				
Physical function (PF2)	100.0 [91.7 – 100.0]	100.0 [80.0 – 100.0]	86.7 [63.3 – 100.0]	0.068
Role function (RF2)	100.0 [100.0 – 100.0]	100.0 [95.8 – 100.0]	100.0 [66.7 – 100.0]	0.067
Emotional function (EF)	83.3 [66.7 – 100.0]	83.3 [66.7 – 91.7]	83.3 [50.0 – 100.0]	0.696
Cognitive function (CF)	100.0 [83.3 – 100.0]	100.0 [83.3 – 100.0]	100.0 [83.3 – 100.0]	0.99
Social function (SF)	100.0 [100.0 – 100.0]	100.0 [95.8 – 100.0]	100.0 [62.5 – 100.0]	0.022
C30 – Symptom scale				
Fatigue (FA)	22.2 [0.0 – 33.3]	22.2 [0.0 – 44.4]	33.3 [8.3 – 58.3]	0.178
Nausea vomiting (NV)	0.0 [0.0 – 16.7]	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.597
Pain (PA)	16.7 [0.0 – 33.3]	16.7 [12.5 – 50.0]	33.3 [16.7 – 50.0]	0.041
Dyspnea (DY)	0.0 [0.0 – 8.3]	0.0 [0.0 – 0.0]	0.0 [0.0 – 33.3]	0.704
Insomnia (SL)	33.3 [0.0 – 66.7]	0.0 [0.0 – 66.7]	33.3 [0.0 – 66.7]	0.878
Appetite loss (AP)	0.0 [0.0 – 0.0]	0.0 [0.0 – 33.3]	0.0 [0.0 – 33.3]	0.098
Constipation (CO)	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.0 [0.0 – 33.3]	0.332
Diarrhea (DI)	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.196
Financial issue (FI)	0.0 [0.0 – 0.0]	0.0 [0.0 – 33.3]	0.0 [0.0 – 41.7]	0.15

BR23 – Functional scale				
Body image (BRBI)	100.0 [81.3 – 100.0]	91.7 [83.3 – 100.0]	95.8 [66.7 – 100.0]	0.571
Sexual function (BRSEF)	33.3 [0.0 – 33.3]	33.3 [16.7 – 33.3]	16.7 [0.0 – 33.3]	0.062
Sexual enjoyment (BRSEE)	16.7 [0.0 – 33.3]	33.3 [0.0 – 33.3]	33.3 [0.0 – 33.3]	0.087
Future perspective (BRFU)	50.0 [25.0 – 100.0]	66.7 [33.3 – 100.0]	66.7 [33.3 – 100.0]	0.972
BR23 – Symptom scale				
Systemic side effects (BRST)	4.8 [0.0 – 10.7]	4.8 [3.6 – 19.0]	14.3 [8.3 – 23.8]	0.025
Breast symptom (BRBS)	12.5 [8.3 – 18.8]	8.3 [0.0 – 33.3]	16.7 [8.3 – 25.0]	0.867
Arm symptom (BRAS)	11.1 [0.0 – 33.3]	11.1 [0.0 – 33.3]	22.2 [8.3 – 44.4]	0.238
Upset by hair loss (BRHL)	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.976

Table 3. Comparison of Quality of Life Domains Across Stages.

Comparison of three independent groups using Kruskal-Wallis independent sample test

Patients with early-stage breast cancer reported the highest median score of 83.3 (IQR 81.3–93.8), followed by those with locally advanced disease with a median of 83.3 (IQR 66.7–91.7). Metastatic patients had the lowest median global health status score of 75.0 (IQR 47.9–83.3). The difference among the three groups was statistically significant (p = 0.004). Physical function scores were highest in early-stage disease (median 100.0, IQR 91.7–100.0) and locally advanced disease (median 100.0, IQR 80.0–100.0), while metastatic patients demonstrated lower scores (median 86.7, IQR 63.3–100.0). Although progressively lower scores were observed with advancing stage, the difference did not reach statistical significance (p = 0.068). Role function scores remained high across all stages (Figure 2).

Figure 2. Radar Plot of Baseline HRQoL Profiles Across Disease Stages in Breast Cancer. This radar plot illustrates baseline health-related quality of life (HRQoL) scores across early-stage, locally advanced, and metastatic breast cancer using the EORTC QLQ-C30 and QLQ-BR23 instruments.

Early-stage and locally advanced groups had identical median scores of 100.0, with narrow IQRs. Metastatic disease showed a wider distribution (median 100.0, IQR 66.7–100.0). The observed differences were not statistically significant (p = 0.067). Emotional function scores were similar across stages, with all groups having a median score of 83.3. Interquartile ranges were widest in metastatic disease (50.0–100.0), but overall differences were not significant (p = 0.696). Cognitive function scores were comparable across early, locally advanced, and metastatic disease groups, each showing a median of 100.0 and overlapping IQRs. No significant difference was observed (p = 0.990). Social functioning showed greater variability. Early-stage patients had a median score of 100.0 (IQR 100.0–100.0), similar to locally advanced disease (median 100.0, IQR 95.8–100.0). Metastatic patients had lower scores (median 100.0, IQR 62.5–100.0). The difference reached statistical significance (p = 0.022).

Fatigue scores increased progressively with disease stage: early (median 22.2), locally advanced (22.2), and metastatic (33.3). However, the difference did not reach statistical significance (p = 0.178). Nausea and vomiting scores were low across all stages, with median scores of 0.0 in all groups. The early-stage group displayed a slightly wider IQR (0.0–16.7). No statistically significant difference was observed (p = 0.597). Pain scores increased with advancing stage. Early-stage patients reported a median of 16.7 (IQR 0.0–33.3), similar to the locally advanced group (16.7, IQR 12.5–50.0). Metastatic patients showed higher scores (33.3, IQR 16.7–50.0). The difference

between groups was statistically significant (p = 0.041). Dyspnea scores were low in all groups, with medians of 0.0. The metastatic group had a wider IQR (0.0–33.3), yet differences remained non-significant (p = 0.704). Insomnia scores demonstrated variability but no significant difference across stages. Medians were 33.3 in early and metastatic disease and 0.0 in locally advanced disease (p = 0.878). Appetite loss scores were generally low, with median values of 0.0 in all groups. Differences were not statistically significant (p = 0.098). Constipation scores were uniformly low across all stages, with median 0.0 and no significant difference (p = 0.332). Diarrhea scores were also low, with median 0.0 in all groups and no significant variation (p = 0.196). Financial difficulty scores were low across stages with no significant differences (p = 0.150). IQRs were wider in metastatic patients, indicating greater variability.

Body image scores were highest in early-stage disease (median 100.0), slightly lower in metastatic (95.8), and lowest in locally advanced disease (91.7). Differences were not statistically significant (p = 0.571). Sexual function scores showed decreasing medians across stages 33.3 in early and locally advanced disease and 16.7 in metastatic but without significant differences (p = 0.062). Sexual enjoyment scores were also similar, with medians of 16.7, 33.3, and 33.3 across the three groups (p = 0.087). Future perspective scores were relatively similar across all stages, with medians ranging from 50.0 to 66.7. Differences were not significant (p = 0.972). Systemic therapy-related symptom scores were lowest in early-stage disease (median 4.8) and highest in metastatic disease (median 14.3). Locally advanced disease had intermediate scores (4.8). The difference among groups reached statistical significance (p = 0.025). Breast symptoms and arm symptoms were comparable across the three groups, with no significant differences (p = 0.867 and p = 0.238, respectively). Medians ranged between 8.3–16.7 for breast symptoms and 11.1–22.2 for arm symptoms. Scores for distress related to hair loss were uniformly 0.0 across all stages, with no observed variation (p = 0.976).

Next, for the four HRQoL parameters presented in Table 4, global health status showed a significant overall difference across stages (Kruskal–Wallis p = 0.004).

Parameter	Early vs. Locally-advanced	Early vs. Metastatic	Locally-advanced vs. Metastatic
	p-value	p-value	p-value
Significant parameters:			
Quality of life (QL2)	0.643	0.009	0.021
Social function (SF)	1	0.056	0.052
Pain (PA)	0.631	0.034	0.204
Systemic side effects (BRST)	0.057	0.064	1

Table 4. Pairwise Comparison of Quality of Life Domains Across Stages Adjusted by Bonferroni Correction for Multiple Tests.

Bonferroni-adjusted pairwise analyses demonstrated significant differences between early-stage and metastatic disease (p = 0.009) and between locally advanced and metastatic disease (p = 0.021). Social functioning showed a significant overall difference (p = 0.022), although no pairwise comparison remained significant after Bonferroni correction. Pain also differed significantly across stages (p = 0.041), with a significant Bonferroni-adjusted difference between early-stage and metastatic disease (p = 0.034). Systemic therapy–related side effects demonstrated a significant overall difference across stages (p = 0.025), but none of the pairwise comparisons met the Bonferroni- adjusted significance threshold.

Discussion

Sociodemographic and clinical context of the cohort

The cohort's baseline characteristics reflect both global breast cancer patterns and local diagnostic realities. All participants were female, and the mean age of 51–55 years aligns with the younger onset typical in Asian and LMIC populations compared with Western settings [11, 12]. The slightly younger age in locally advanced and metastatic groups likely reflects delayed detection associated with limited screening access and socioeconomic barriers [13]. Educational attainment varied across stages, highlighting heterogeneity in health literacy and access to care. The presence of advanced disease even among higher-educated women suggests that structural barriers rather than individual knowledge continue to impede early diagnosis [14]. Employment was low across all groups, with the highest unemployment in metastatic disease, consistent with functional limitations and financial strain in advanced cancer [15]. Marital status patterns mirrored regional demographics, though the higher proportion of widowed or single individuals in the locally advanced group may indicate reduced social support, a known factor in delayed help-seeking [16, 17]. Comorbidities such as hypertension and diabetes were common, particularly in early-stage patients. This may reflect more frequent healthcare engagement, facilitating earlier detection, whereas those presenting with metastatic disease may have had limited prior health-system contact [18]. These metabolic comorbidities may also influence disease biology and treatment tolerance [19]. Differences in treatment history aligned with clinical staging. Almost all early-stage patients had undergone surgery, while locally advanced and metastatic groups had greater exposure to systemic therapy, consistent with neoadjuvant or palliative treatment pathways. Low radiotherapy use across stages likely reflects treatment sequencing and timing relative to HRQoL assessment.

Tumor histopathology and molecular profile

The histopathologic distribution in this cohort mirrors global patterns, with IDC comprising the vast majority of tumors across all stages [20]. IDC represented all early- stage cases and remained dominant in locally advanced and metastatic disease. The slightly higher proportion of mixed IDC–ILC tumors in metastatic patients may reflect the more infiltrative biology of lobular components, which can be underdiagnosed at initial presentation and are prone to diffuse spread [21]. The presence of miscellaneous histologies, although limited, highlights real-world heterogeneity and the importance of accurate pathological classification. Tumor grade patterns also align with expected biology. Grade II and III tumors predominated across stages, with high-grade lesions most common in locally advanced disease, consistent with more aggressive tumor behavior and potentially delayed detection [22]. Metastatic disease showed a comparatively higher proportion of grade II tumors, underscoring that histologic grade alone does not fully predict metastatic potential. The substantial number of unknown grades particularly in metastatic patients likely reflects limited tissue availability or incomplete diagnostic workups in advanced presentations.

The IHC subtype distribution underscores the molecular diversity of breast cancer. Luminal B (HER2– and HER2+) subtypes were most frequent in locally advanced and metastatic groups, consistent with their higher proliferative activity and tendency to present at more advanced stages [23]. Luminal A tumors were more common in early-stage disease, aligning with their slower growth and higher likelihood of being detected earlier through screening. HER2-enriched tumors were most prevalent in early-stage disease but rare in metastatic patients, possibly reflecting early detection of fast-growing HER2-positive lesions or effective earlier treatments limiting progression. HER2-low tumors were present across all stages but remained a minority, highlighting the growing importance of precise HER2 quantification as therapeutic options expand [24]. TNBC prevalence was relatively low overall, though slightly higher in advanced stages. While TNBC is often associated with late presentation, its modest representation here suggests population-specific molecular epidemiology and indicates that other aggressive subtypes particularly Luminal B contribute significantly to advanced-stage burden [4].

Finally, the notable proportion of unknown IHC results in locally advanced and metastatic groups underscores persistent challenges in obtaining complete biomarker profiles in resource-limited

settings. Variability in tissue sampling, fragmented diagnostic pathways, and inconsistent access to IHC testing may contribute to these gaps, which can directly impact therapeutic decision-making. These missing values were categorized as “unknown” for descriptive purposes but were not used in inferential analyses, as HRQoL comparisons were based on disease stage rather than tumor subtype or grade. Although a formal sensitivity analysis was not conducted, the missingness is unlikely to affect the primary findings because subgroup analyses by molecular or histologic features were not part of the study objectives. Nevertheless, more complete biomarker profiling in future research would enable deeper biological interpretation.

Stage-dependent quality-of-life patterns

The stage-stratified QoL analysis revealed several important patterns, although only some remained statistically significant after Bonferroni correction. Global health status differed significantly across stages and showed meaningful pairwise differences between both early-stage and metastatic disease and between locally advanced and metastatic disease. Metastatic patients reported the lowest scores, consistent with prior evidence that increased tumor burden is associated with poorer overall well-being even before systemic therapy begins [25]. The wide score distribution in the metastatic group underscores the heterogeneity of late-stage disease experiences in real-world settings. Functional domains demonstrated mixed patterns. Physical functioning showed a gradual decline from early to metastatic disease, while role functioning remained relatively high but more variable among metastatic patients. Emotional and cognitive functioning were similar across stages, as seen in other HRQoL studies. However, this stability should be interpreted cautiously, as it may reflect ceiling effects of the EORTC scales, cultural reluctance to disclose psychological distress, or limited statistical power rather than true preservation of psychological resilience. Social functioning showed a significant overall difference across stages, but pairwise contrasts did not remain significant after Bonferroni adjustment, suggesting that the apparent decline with advancing stage should be viewed as a trend rather than a definitive stage-associated change.

Symptom burden also varied across stages. Pain showed a significant overall difference, and the early-stage versus metastatic comparison remained significant after correction [26, 27]. Fatigue demonstrated an upward trend but was not statistically different after adjustment, consistent with the multifactorial and variable nature of fatigue in untreated cancer. Other systemic symptoms nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea remained low across groups, which is expected in a pre-treatment cohort. Financial difficulties showed greater variability in metastatic patients but did not reach significance after adjustment. Breast cancer–specific QoL domains reflected additional nuances. Body image remained generally high but was slightly lower in locally advanced disease, potentially due to visible tumor changes, while sexual function and enjoyment were lowest in metastatic patients [28, 29]. Cultural context may also influence these domains. In Indonesia, discussions of intimacy and emotional distress are often restrained, which may contribute to lower or more uniform scores in sexuality-related items regardless of stage [30]. Although cultural influences were not directly assessed, acknowledging them is important when interpreting self-reported HRQoL in conservative sociocultural settings. Systemic therapy–related side effects differed significantly overall but showed no significant pairwise differences after Bonferroni correction, suggesting that the observed pattern should be interpreted as a general trend rather than a stage-specific effect. Breast and arm symptoms showed no meaningful variation across stages.

To enhance the clinical relevance of these findings, absolute differences between stages were compared with published minimally important differences (MIDs) for the QLQ-C30. Reported MIDs for within-group change typically range from 5 to 14 points for improvement and −14 to −4 points for deterioration, while between- group MIDs generally fall between 4 and 11 points for improvement and −18 to −4 points for deterioration; correlation-weighted estimates for most QLQ-C30 scales cluster around 4–10 points in absolute value [31]. In this study, metastatic patients had an 8.3-point lower median global health status compared with early-stage patients, a difference that

falls within established MID ranges and may be clinically meaningful. Pain scores were 16.6 points higher in metastatic compared with early-stage disease exceeding typical MID thresholds and indicating a likely meaningful increase in symptom burden. Systemic therapy–related symptoms were approximately 10 points higher in metastatic disease, aligning with small-to- moderate MIDs. Social functioning showed substantial variability, with lower quartile differences approaching −37.5 points; however, given the absence of statistically significant pairwise differences after adjustment, this finding should be interpreted cautiously.

Study Limitations

This study has several important limitations. First, the cross-sectional design captures HRQoL at a single pre-treatment time point, preventing assessment of temporal changes or causal relationships between disease stage and patient-reported outcomes. Second, although the total sample exceeded the calculated minimum, subgroup sizes particularly in the early-stage cohort were modest. As a result, the analysis relied on unadjusted non-parametric comparisons, and multivariable modeling was not performed to avoid overfitting and unstable estimates. HRQoL differences across stages should therefore be interpreted in the context of baseline variation in age, education, comorbidities, and prior treatment, all of which may influence reported outcomes. Third, real-world constraints led to incomplete pathological and biomarker data (e.g., unknown tumor grade or IHC subtype in several advanced-stage cases), which may limit detailed biological interpretation. Fourth, prior treatments especially surgery or earlier systemic therapy were present in a substantial proportion of participants and may have affected certain HRQoL domains, despite assessments being conducted before the initiation of new systemic therapy. Fifth, the study did not include dedicated measures of psychological distress such as validated anxiety or depression scales (e.g., HADS, PHQ-9, GAD-7). As a result, we could not quantify or adjust for mood disorders, which are known strong determinants of HRQoL, and this may partly contribute to similarities observed in emotional and cognitive functioning across stages. Finally, the study was conducted in two referral centers within a single region of Indonesia, which may limit generalizability to other LMIC settings with different healthcare structures or sociocultural contexts. Future research with larger, more diverse cohorts and longitudinal follow-up is needed to clarify the independent contribution of disease stage to HRQoL and to explore how baseline HRQoL influences treatment tolerance and longer-term outcomes.

Clinical Insights and Future Direction

This study highlights how breast cancer stage at presentation can shape the patient experience even before systemic therapy begins. Although stage-dependent differences in survival and treatment response are well documented, fewer studies in LMIC settings have examined how sociodemographic context and tumor biology intersect with multidimensional HRQoL. In this cohort, advanced-stage disease was associated with younger age at presentation, more aggressive tumor features particularly Luminal B subtypes and high-grade carcinomas and significantly lower global health status and higher pain scores compared with earlier stages, based on Bonferroni-adjusted analyses. Other HRQoL domains, including social functioning and systemic therapy–related symptoms, showed overall differences across stages but did not retain statistical significance in pairwise comparisons, indicating more modest or variable stage-related patterns. These findings suggest that the burden of advanced breast cancer may begin before treatment initiation and highlight the need for earlier detection and supportive care approaches tailored to patients with higher symptom burden. A key strength of this cohort is the integration of detailed pathological data with HRQoL assessment, allowing a more comprehensive view of how tumor characteristics relate to patient-reported experience. The combination of high unemployment, varied educational attainment, and common comorbidities indicates that social determinants may further shape HRQoL at presentation. Meanwhile, the predominance of aggressive molecular subtypes in advanced disease reflects a dual challenge of delayed diagnosis and unfavorable tumor

biology. Together, these observations reinforce that improving patient outcomes requires addressing both clinical and structural factors that influence when and under what circumstances women seek and access care.

These insights support several practical actions. First, strengthening early detection efforts through community-based education, risk communication, and accessible clinical breast examinations may help shift diagnoses toward earlier stages [32]. Second, incorporating routine HRQoL assessments into baseline oncology visits can identify patients who would benefit from early palliative care, psychological support, or pain management [33]. Third, improving the completeness and timeliness of biomarker testing, especially in advanced disease, may reduce treatment delays and optimize therapy selection [34]. Finally, further research should evaluate how pre-treatment HRQoL influences treatment tolerance, hematologic toxicity, and survival, enabling more personalized care pathways. By integrating biological, clinical, and psychosocial dimensions, these findings provide a foundation for developing stage-tailored care models that address both symptom burden and broader determinants of patient well-being across diverse healthcare settings.

In conclusion, in this cohort, advancing disease stage was associated with trends toward more aggressive tumor characteristics and lower HRQoL scores prior to the initiation of a new line of systemic therapy. Patients with locally advanced and metastatic disease demonstrated significantly lower global health status compared with earlier stages, and metastatic patients reported significantly higher pain scores. Other domains such as social functioning and systemic therapy–related symptoms showed overall stage differences but did not retain statistical significance in pairwise comparisons, indicating that these patterns should be viewed as exploratory. Given the modest subgroup sizes and cross-sectional design, these findings warrant cautious interpretation but suggest that individuals presenting with advanced disease may experience greater symptom burden at baseline. Incorporating routine HRQoL assessment and considering stage-specific supportive needs during initial oncology evaluation may help identify vulnerable patients and guide more holistic care planning. Continued efforts to promote earlier diagnosis and strengthen supportive-care pathways may ultimately improve treatment readiness and overall well-being across the breast cancer continuum.

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Declarations

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Clinical trial registration

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Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding authors per reasonable request.

Code availability

Not applicable

Authors' contributions

HS: Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing. MS: Conceptualization, Writing - Original Draft, Writing

- Review & Editing, Supervision. EH: Writing - Original Draft, Writing - Review & Editing, Supervision. AA: Writing - Original Draft, Writing - Review & Editing, Supervision

Ethics approval

Ethical approvals were obtained from the institutional review boards of both participating hospitals (197/ KEP/2024 from Universitas Airlangga Hospital and 445/02/KOM.ETIK/2025 from Haji General Hospital).

Consent to participate

Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Originality declaration for figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

Declaration on generative AI and AI-assisted technologies in the writing process

Not applicable.

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