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# Association of Ki-67 Proliferation Index with Intrinsic Subtypes of Male Breast Cancer in a Ugandan Cohort

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## ABSTRACT

Globally, male breast cancer (MBC) is an infrequent disease presentation that carries a poorer outlook relative to its female counterpart; nonetheless, published research on MBC is sparse, particularly within resource-constrained environments. Our goal was to investigate Ki-67 expression and its links to clinicopathological parameters and intrinsic subtypes in a cohort of male breast cancer (BC) patients from a setting with limited resources. A cross-sectional methodology was utilized, drawing upon retrospectively collected information. Data were analyzed for 54 male BC cases diagnosed over an 11-year window from January 2014 to December 2024. The work was undertaken within the Department of Pathology at the Uganda Cancer Institute (UCI) in Kampala, Uganda, spanning February to June 2025. Information was sourced from electronic repositories, patient medical charts, and laboratory requisition forms. To evaluate the relationship between the absolute Ki-67 value (mean) and the clinical/pathological features, as well as BC intrinsic subtypes, a one-way analysis of variance was employed; this was followed by multivariable linear regression modeling to control for potential confounders. The cohort's average age stood at 56.4 ± 15.1 years, and the youngest individual was 25 years old. Advanced disease (stage III and IV) was present in 68.5% (38/54) of patients. Correspondingly, the ER+, PR+, and HER2− intrinsic subtype was the dominant category, accounting for 68.5% (37/54) of tumors. Following adjustment via multivariable linear regression, solely the intrinsic BC subtypes (95% confidence interval [CI] = 3.397-16.503, P = .032) and PR status (95% CI = 5.693-24.397, P = .042) persisted as significant determinants of Ki-67 expression. Our results reveal elevated expression in MBC tumors that are triple-negative or lack PR expression. This observation suggests that elevated Ki-67 expression in MBC may serve as a marker for categorizing male BC patients by tumor aggressiveness.

**Keywords:** Males, Breast cancer, Intrinsic subtypes, Ki-67 Expression

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## Introduction

Male breast cancer (MBC) persists as the least frequently encountered cancer type when set against female breast cancer (FBC), which holds the top rank among malignancies affecting women worldwide [1]. MBC is responsible for under 1% of the overall breast cancer (BC) burden globally [2, 3]. The estimated worldwide incidence rate ranges from 0.5 to 1.0 per 100,000 [4]. Despite its rarity relative to FBC, recent trends point toward a rise in both the frequency of new MBC diagnoses and associated deaths [5]. Across Europe, incidence figures are broadly pegged at fewer than 3 new cases per 100,000 men, while mortality hovers at fewer than 1 death per 100,000 men, with country-specific differences [4]. Data indicate that both MBC and FBC incidence runs higher among populations of African American and African ancestry, with rates documented at 1.4% and 4.2%, respectively [6]. Within Uganda, research from the Northern region found that the MBC proportion was 6.2% of all BCs in that

region. A separate investigation centered on the Central region put the figure at 1.4% of total BC cases [7]. These figures suggest that MBC occurrence can fluctuate across different geographic zones within the country [8].

Literature describing the intrinsic subtype profiles of MBC is extremely limited, a gap that is especially pronounced in low- and middle-income countries (LMICs) such as Uganda. The existing MBC-focused research emerging from LMICs has largely centered on outlining basic clinicopathological features. Examinations of hormone receptors (HRs) and human epidermal receptor 2 (HER2) status in MBC within these settings reveal that the majority of tumors stain positive for estrogen receptor (ER) and progesterone receptor (PR) when contrasted with FBCs [9, 10]. This pattern is attributed to the elevated vulnerability of men whose circulating estrogen exceeds normal concentrations while testosterone dips below typical levels [11]. The ER+, PR+, and HER2− (luminal A) intrinsic subtype is widely accepted as the predominant BC subtype among the four intrinsic MBC categories, representing over 75% of cases, with ER+, PR+/−, and HER2+/− (luminal B) trailing [6, 12-14]. Luminal B likewise makes up a considerable share of MBC, and certain studies have even positioned ER+, PR+/−, and HER2+/− as the single most common intrinsic BC subtype [15]. HER2-enriched (HER2-E) and triple-negative breast cancer (TNBC, also termed basal-like) make up an even tinier slice of MBCs compared with FBCs [16-18].

Measuring biomarkers such as Ki-67 in BC enables clinicians to categorize patients by expression levels, providing information that sheds light on tumor aggressiveness and the potential for disease progression. Among the panel of prognostic tools available for malignancy management, BC included, Ki-67 has emerged as a particularly useful marker. It serves as a readout of proliferative activity within tumor cells, and importantly, the fraction of Ki-67-positive cells has demonstrated utility in dissecting survival patterns specific to MBC. An elevated Ki-67 proliferative index correlates with poorer overall survival in MBC [19, 20]. Conversely, a low proliferation rate points toward indolent tumor kinetics and diminished aggressive behavior. Published evidence indicates that tumors with the ER+, PR+, and HER2− phenotype tend to exhibit lower Ki-67 indices than tumors with other subtypes. Beyond this, it is well established that HER2-E and TNBC, recognized as the most clinically aggressive among the intrinsic BC categories, exhibit markedly higher Ki-67 expression than their luminal counterparts [21, 22].

Within the Ugandan context, the body of evidence documenting the molecular portrait of MBC intrinsic subtypes and their interplay with Ki-67 expression remains strikingly thin. The country also grapples with insufficient diagnostic infrastructure for oncology patients, resulting in a preponderance of late-stage diagnoses at the time of diagnosis. Protracted intervals before a cancer diagnosis is established are commonplace, and these are further complicated by treatment barriers encompassing the exorbitant costs of chemotherapeutic regimens and erratic drug supply chains. The plight of MBC patients is amplified by a widespread lack of disease awareness among the general populace. These intersecting factors collectively account for the paucity of investigative work focused on MBC, notwithstanding the few published accounts that have described intrinsic subtype features of MBC arising from LMIC settings, Uganda among them. Equally, there is a pronounced deficiency in data on prognostic factor assessment—routine parameters included—specifically in Ugandan MBC cases. Driven by these knowledge gaps, the current study was conceived with the primary objective of using immunohistochemistry (IHC) to profile the intrinsic subtypes encountered in MBC. A secondary objective entailed probing Ki-67 expression levels and delineating their relationships with intrinsic BC subtypes alongside an array of additional clinicopathological attributes within a male BC case series.

## Materials and Methods

### *Study design and setting*

The investigation employed a cross-sectional design that drew on retrospectively assembled records from male individuals diagnosed with BC spanning the period from January 2014 to December 2024. The execution of the study spanned from February-November 2024 to March 2025-June 2025 and was situated within the Department of Pathology at the Uganda Cancer Institute (UCI) in Kampala, Uganda. The bulk of the specimens processed by this department originate from Mulago National Hospital (MNH), the country's principal referral institution. That said, submissions are also received from a range of other healthcare establishments within the Kampala metropolitan area and outlying regions, as well as from cross-border sources, notably South Sudan and Kenya. The UCI holds the distinction of being the largest cancer care and research facility serving the East African corridor.

*Study population*

The subject pool comprised male patients with a BC diagnosis recorded within the January 2014 to December 2024 timeframe. Enrollment was contingent upon being male with a histologically confirmed BC diagnosis and the availability of a formalin-fixed paraffin-embedded (FFPE) tissue block of adequate quality. Excluded from the dataset were all female BC diagnoses, instances where tissue blocks could not be located, FFPE blocks rendered unusable due to insect damage, and MBC cases referred from bordering nations, specifically South Sudan and Kenya.

*Sample size estimation and sampling procedure*

Given the inherently low frequency of this malignancy, a convenience-based sampling strategy was necessitated, as probability-driven sampling approaches were not feasible. Accordingly, all cases meeting the stated inclusion criteria were recruited consecutively. Following this process, a final tally of 54 cases satisfied all eligibility conditions and were retained for analysis.

*Histopathological re-evaluation of the selected cases*

A histological reassessment was performed on all selected cases. The FFPE tissue blocks were sectioned at 4 μm, after which de-waxing was performed by placing the sections in a microwave oven set to 60 °C for 50 minutes. Clearing was then proceeded through two consecutive xylene baths, with 10 dips executed per bath. Rehydration involved 10 dips through a descending ethanol gradient (100%, 95%, 80%, and 70%) followed by a rinse under flowing tap water and, ultimately, staining with standard hematoxylin and eosin (H&E) reagents. Microscopic evaluation of the prepared slides was carried out using a light microscope (Olympus Corporation, CX31RBSF Model, Tokyo, Japan) by two pathologists operating independently (JJY and TO). When their assessments diverged, a consensus score was reached through mutual deliberation. The histopathological classification scheme applied to BC in this work was drawn from the publication by Rakha *et al*. [23]. Likewise, tumor grade and stage were assigned according to the College of American Pathologists (CAP) protocols [24].

*Immunohistochemical staining of Ki-67*

The assessment of Ki-67 relied upon IHC-processed FFPE tissue sections. Staining with the MIB-1 antibody directed against Ki-67 was interpreted at a magnification of ×400, with attention concentrated on “hot spot” zones. The percentage of positively staining cells was determined by manual enumeration of at least 1000 tumor cells across high-power fields at ×400 magnification, as established practice [25]. All nuclei displaying brown chromogen deposition, without regard to the intensity of the stain, were recorded as positive events. A threshold of $\leqslant$ 20% was adopted for Ki-67, consistent with the St. Gallen Consensus Guidelines [26] and findings reported by Dokcu *et al*. [22]. The relationship between Ki-67 expression and both the intrinsic BC subtypes and a range of clinical-pathological parameters was explored to gauge disease aggressiveness, a parameter reflected by the Ki-67-measured proliferative drive of the tumor. Expression was dichotomized into low (< 20%) and high ($\geqslant$ 20%) strata because such a demarcation has predictive value for BC patient survival and is associated with other adverse prognostic features, despite the enduring lack of consensus regarding its routine clinical deployment [27].

*Immunohistochemical staining of ER, PR, and HER2*

Tissue blocks were cut at 4 μm and affixed to adhesive-treated glass slides (FrostStat, DAKO-Denmark), then deparaffinized on a heated plate at 50°C for 30 minutes. The slides were subsequently exposed to microwave irradiation at 750 watts for 10 minutes while immersed in a 10 mmol/L tris-buffered solution at pH = 7.0, in keeping with previous methodology [28]. Following this step, the FFPE tissue sections were submerged in a 3% $H_2O_2$ solution for 10 minutes to neutralize endogenous peroxidase activity, thereby minimizing nonspecific background signal. Rinsing in phosphate-buffered solution was performed, followed by pretreatment with a secondary antibody amplifier conjugated to horseradish peroxidase and a subsequent buffer wash. Incubation with monoclonal mouse antibodies targeting ER, PR, and HER2 (manufactured by DAKO, Denmark) was performed for 30 minutes at ambient temperature. For the detection step, diaminobenzidine tetrahydrochloride (DAKO LSAB2, Denmark) solution was layered onto the sections for 10 seconds. Counterstaining was performed with Harris hematoxylin for 30 seconds, followed by 10 dips in each of two xylene changes to achieve clearing. Final mounting was done using DPX medium and coverslipping. The interpretation and documentation of IHC-stained slides followed previously outlined protocols [28].

*Molecular subtyping of BC and assessment of PR-negative status*

Four distinct intrinsic BC subtypes served as the basis for categorization in this work: ER+, PR+, and HER2− (luminal A); ER+, PR+/−, and HER2+/− (luminal B); HER2-enriched (HER2-positive); and TNBC, consistent with classification approaches applied elsewhere [29]. A supplementary focus was on scrutinizing the magnitude of PR-negative status among the study subjects.

*Data collection procedure*

A structured data-capture instrument, developed specifically for this investigation, was used to retrieve information. Its layout incorporated 3 discrete sections (capturing independent variables): one devoted to demographic and clinical metrics (chronological age, length of illness, affected side, tumor burden stage, and therapeutic interventions received), another detailing pathological descriptors (histological variants of BC, tumor differentiation grades, and lymph node involvement [LNI]), and a third documenting IHC profiles (ER, PR, HER2, and intrinsic BC subtypes). Ki-67 expression represented the outcome variable of interest among the immunohistochemical measurements. Source materials from which data points were drawn included the electronic information system, individual patient medical charts, and accompanying laboratory submission documents; all extracted items were subsequently logged into the designated data sheet. Upon merging the information from both streams, the compiled dataset was carefully examined to eliminate overlapping entries.

*Statistical analysis*

Data processing and statistical computation relied on the Statistical Package for Social Sciences software, version 22.0 (IBM Corp., Armonk, New York). Cleaning routines targeting incomplete fields, duplicate records, and inaccurately keyed values were executed by generating frequency runs, percentage breakdowns, and cross-tabulation matrices. Presentation of descriptive findings, encompassing the clinical, pathological, and immunohistochemical landscape of the patient group, using frequencies alongside corresponding percentages. For continuous variables, summary statistics were reported as mean ± standard deviation (SD). The relationship between absolute Ki-67 measurements and the remaining clinical-pathological factors was evaluated using a one-way analysis of variance (ANOVA). Conformity of Ki-67 expression values to a Gaussian distribution was verified through the Shapiro-Wilk procedure, whereby P-values exceeding .05 signified sufficient normality. All independent variables yielding $P < .2$ in the one-way ANOVA were included in a multivariable linear regression model to mitigate confounding. Levene's test was applied to the categorical variables to confirm the assumption of homogeneity of variance across groups. The threshold for declaring statistical significance was set at a two-tailed P-value of less than .05. Adherence to the STROBE recommendations governing observational research reporting was maintained throughout [30].

**Results and Discussion**

*Selection process of the cases for analysis*

The sequence in which cases progressed toward final inclusion in the analysis is shown in **Figure 1.** Across the full decade of histological diagnoses, breast-related pathologies represented 28.7% (1403/4895) of the total, and within that subset, benign breast entities constituted 5.6% (78/1403). Of the malignant breast diagnoses, the overwhelming preponderance—95.4% (1264/1325)—were FBC, whereas MBC comprised 4.6% (61/1325). Of the MBC pool, 54/61 cases ultimately met the eligibility criteria and were retained for analysis.

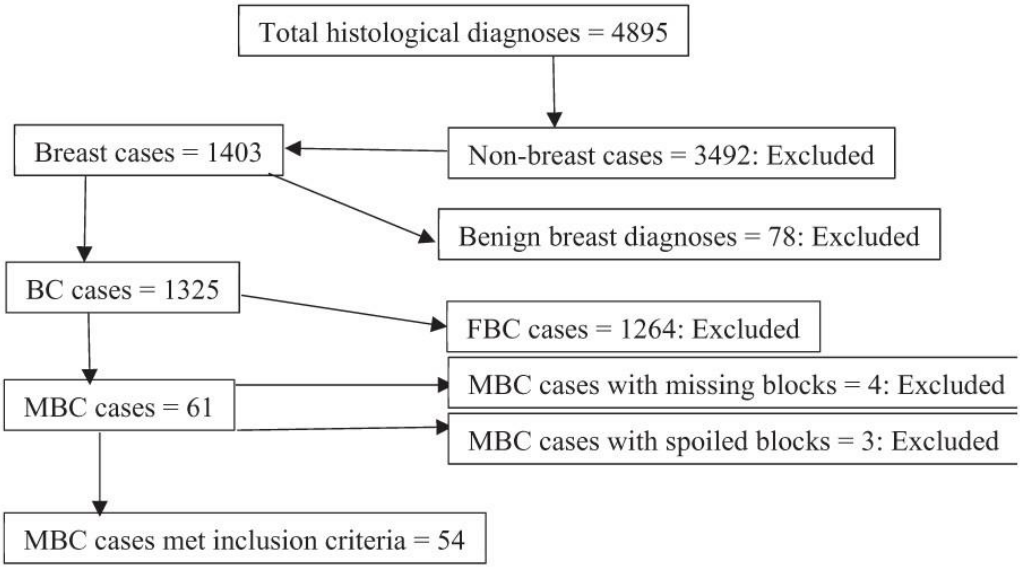


**Figure 1.** Flowchart indicating the selection process for the MBC cases in the study. Abbreviations: BC = breast cancer; MBC = male breast cancer; FBC = female breast cancer.

*Clinical and pathological characteristics of the patients*

The average age computed for the cohort was 56.4 ± 15.1 years, with individuals aged 60 years and beyond accounting for the largest proportion at 40.7% (22/54). The left breast was the site of disease in exactly one-half, 50.0% (27/54), of the patients studied. A notable segment (42.6%; 23/54) had lived with manifestations of their illness for more than 5 months before seeking medical evaluation; the mean interval from symptom onset to presentation was 7.0 ± 3.0 months. Diseases at an advanced stage (stage III or IV) were documented in the majority (68.5%, 38/54). Infiltrating ductal carcinoma was, by a wide margin, the prevailing histological pattern, seen in 85.2% (46/54) of the analyzed tumors. Moderately differentiated lesions (grade 2) were observed in 48.1% (26/54) of the group **(Table 1).**

**Table 1.** Demographic, clinical, and pathological characteristics of the patients (n = 54).

| Characteristics | Proportion (%) | Count (n) |
|---|---|---|
| **Age group (years)** | | |
| **25–39** | 9.3 | 5 |
| **40–49** | 22.2 | 12 |
| **50–59** | 27.8 | 15 |
| **≥ 60** | 40.7 | 22 |
| **Tumor laterality** | | |
| **Left side** | 50.0 | 27 |
| **Right side** | 46.3 | 25 |
| **Bilateral involvement** | 3.7 | 2 |
| **Duration before seeking care (months)** | | |
| **2–5** | 40.7 | 22 |
| **6–10** | 42.6 | 23 |
| **> 10** | 16.7 | 9 |
| **Tumor size (cm)** | | |
| **≤ 2.0** | 0.0 | 0 |
| **2.1–5.0** | 44.4 | 24 |
| **> 5.0** | 35.2 | 19 |
| **Not available** | 20.4 | 11 |
| **Clinical stage** | | |
| **Stage I** | 0.0 | 0 |
| **Stage II** | 11.1 | 6 |
| **Stage III** | 31.5 | 17 |
| **Stage IV** | 37.0 | 20 |

| | | |
|---|---|---|
| **Not available** | 20.4 | 11 |
| **Type of surgery** | | |
| **Simple mastectomy** | 11.1 | 6 |
| **Radical mastectomy** | 13.0 | 7 |
| **Modified radical mastectomy** | 35.2 | 19 |
| **No surgical intervention** | 40.7 | 22 |
| **Nodal status** | | |
| **pN0** | 61.1 | 33 |
| **pN1** | 7.4 | 4 |
| **pN2** | 5.6 | 3 |
| **pN3** | 9.3 | 5 |
| **Not available** | 16.7 | 9 |
| **Histopathological classification** | | |
| **Invasive ductal carcinoma** | 85.2 | 46 |
| **Invasive lobular carcinoma** | 13.0 | 7 |
| **Intracystic papillary carcinoma** | 1.9 | 1 |
| **Tumor grade** | | |
| **Grade 1** | 18.5 | 10 |
| **Grade 2** | 48.1 | 26 |
| **Grade 3** | 33.4 | 18 |

*Clinical features of the patients*

The range of presenting complaints observed among the studied patients is summarized in **Figure 2.** Topping the list of clinical manifestations was a nontender subareolar mass, the chief finding in 74.1% (40/56) of cases. Enlarged lymph nodes constituted the second most commonly recorded clinical sign, present in 22.2% (12/56) of the cohort. Gynecomastia as a mode of presentation was distinctly uncommon, encountered in only 3.7% (2/54) of cases.

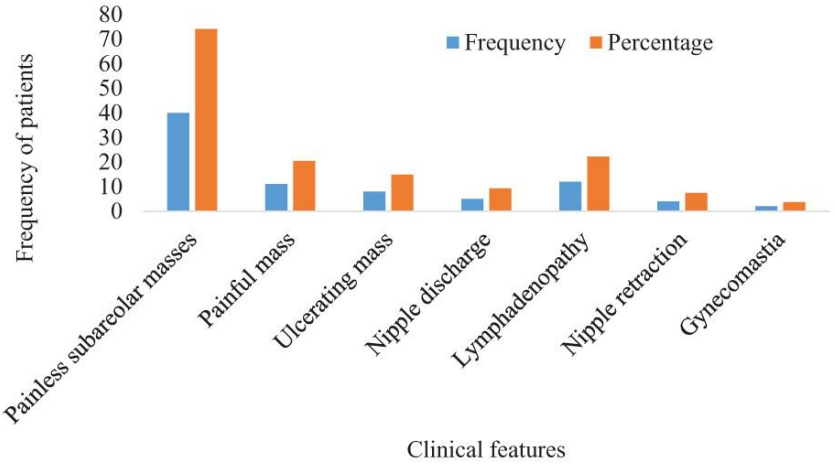


**Figure 2.** Clinical features of males with BC.

*ER, PR, HER2, and Ki-67 expression, and intrinsic subtypes of BC*

Staining positivity for ER was demonstrated in 92.6% (50/54) of tumor samples; PR expression was confirmed in 74.1% (40/54); and HER2 overexpression was detected in merely 5.6% (3/54). When grouped by intrinsic subtype, the ER+, PR+, and HER2− category was the most abundant, accounting for 68.5% (37/54) of all cases, ahead of the ER+, PR+/−, and HER2+/− group, which accounted for 16.7% (9/54). The HER2+-enriched variant accounted for 5.6% (3/54). Triple-negative breast cancer was the designation applied to 9.2% (5/54) of the cohort. Values for Ki-67 expression centered on a mean of 35.2 ± 18.0%, with the lowest and highest levels observed at 10% and 70%, respectively. Slightly under half, 46.3% (25/54), of the specimens exhibited Ki-67 expression in the low range (⩽ 20%), whereas the high expression range (> 20%) included the remaining 53.7% (29/54) **(Table 2).** The distribution of Ki-67 positivity values within each tumor grade grouping is shown in a box plot **(Figure 3).**

**Table 2.** ER, PR, HER2, and Ki-67 expression, and intrinsic subtypes of BC (n = 54).

| Parameters | Percentage (%) | Number (n) |
|---|---|---|
| **Estrogen receptor (ER) status** | | |
| **Positive** | 92.6 | 50 |
| **Negative** | 7.4 | 4 |
| **ER nuclear staining intensity** | | |
| **Weak** | 20.4 | 11 |
| **Moderate** | 25.9 | 14 |
| **Strong** | 46.3 | 25 |
| **Absent** | 7.4 | 4 |
| **Progesterone receptor (PR) status** | | |
| **Positive** | 74.1 | 40 |
| **Negative** | 25.9 | 14 |
| **PR nuclear staining intensity** | | |
| **Weak** | 1.9 | 1 |
| **Moderate** | 46.3 | 25 |
| **Strong** | 25.9 | 14 |
| **Absent** | 25.9 | 14 |
| **HER2 receptor status** | | |
| **Positive** | 5.6 | 3 |
| **Negative** | 94.4 | 51 |
| **HER2 membrane staining intensity** | | |
| **Weak (+1)** | 27.8 | 15 |
| **Equivocal (+2)** | 3.7 | 2 |
| **Strong (+3)** | 5.6 | 3 |
| **Negative** | 63.0 | 34 |
| **Breast cancer intrinsic subtypes** | | |
| **ER+, PR+, HER2−** | 68.5 | 37 |
| **ER+, PR+/−, HER2+/−** | 16.7 | 9 |
| **HER2-enriched (ER−, PR−, HER2+)** | 5.6 | 3 |
| **Triple-negative (basal-like) (ER−, PR−, HER2−)** | 9.2 | 5 |
| **Ki-67 proliferation index** | | |
| **Low (≤20%)** | 46.3 | 25 |
| **High (>20%)** | 53.7 | 29 |

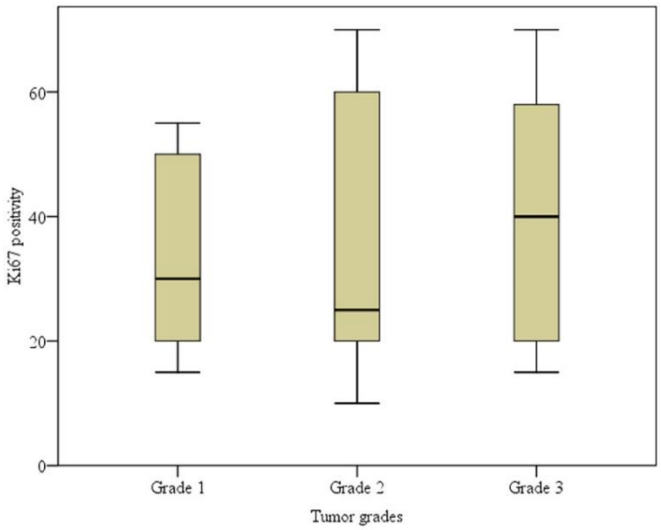


**Figure 3.** Distribution of Ki-67 positivity by tumor grade.

*Association of Ki-67 expression with patients' clinical, pathological, and immunohistochemical characteristics*

A strong statistical association was identified between loss of PR expression and an increase in Ki-67 levels (F-statistic = 8.937, P = .004). Specimens carrying a triple-negative breast cancer designation likewise demonstrated

a significant tie to higher Ki-67 values (F-statistic = 3.157, P = .033). Additionally, comparisons of group averages for ER expression (F-statistic = 3.014, P = .088) and chronological age (F-statistic = 2.885, P = .085) approached conventional levels of significance. Age itself showed no meaningful relationship (P = .734) **(Table 3).** When age, tumor stage, ER status, PR status, and intrinsic BC subtypes were incorporated into a multivariable linear regression model to account for their potential confounding effects **(Table 4),** the only variables to emerge as enduring independent correlates of Ki-67 expression were the intrinsic BC subtypes (95% CI = 3.397-16.503, P = .032) and PR status (95% CI = 5.693-24.397, P = .042). This outcome indicates that average Ki-67 expression levels differ significantly by PR status and intrinsic BC subtype.

**Table 3.** The association between absolute Ki-67 values and clinical, pathological, and immunohistochemical characteristics.

| Variables | N | P-value | F-statistic | 95% CI | Mean ± SD |
|---|---|---|---|---|---|
| **Age, y** | | .085 | 2.885 | | |
| **25-40** | 5 | | | 10.80-31.20 | 21.0 ± 8.2 |
| **41-59** | 27 | | | 32.70-47.15 | 39.9 ± 18.3 |
| **⩾ 60** | 22 | | | 24.94-40.52 | 32.7 ± 17.6 |
| **Tumor grades** | | .651 | 0.433 | | |
| **Grade 1** | 10 | | | 22.18-44.82 | 33.5 ± 15.8 |
| **Grade 2** | 26 | | | 26.02-41.29 | 33.7 ± 18.9 |
| **Grade 3** | 18 | | | 29.39-47.61 | 38.5 ± 18.3 |
| **Tumor stages** | | .126 | 1.988 | | |
| **Stage 2** | 6 | | | 13.22-51.78 | 32.5 ± 18.4 |
| **Stage 3** | 17 | | | 19.91-34.80 | 27.4 ± 14.5 |
| **Stage 4** | 20 | | | 32.60-48.20 | 40.4 ± 16.7 |
| **Missing data** | 11 | | | - | - |
| **Histological types** | | .738 | 0.113 | | |
| **Infiltrating ductal carcinoma** | 44 | | | 30.24-41.03 | 35.6 ± 17.7 |
| **Others** | 10 | | | 19.19-47.81 | 33.5 ± 20.0 |
| **Lymph node involvement** | | .562 | 0.583 | | |
| **Yes** | 12 | | | 21.32-42.01 | 31.7 ± 16.3 |
| **No** | 33 | | | 30.62-44.11 | 37.4 ± 19.0 |
| **Missing data** | 9 | | | - | - |
| **Disease duration, mo** | | .565 | 0.578 | | |
| **2-5** | 22 | | | 28.08-44.92 | 36.5 ± 1 9.0 |
| **6-10** | 23 | | | 25.02-39.76 | 32.4 ± 17.0 |
| **>10** | 9 | | | 25.01-53.88 | 39.4 ± 18.8 |
| **ER expression** | | .088 | 3.014 | | |
| **Positive** | 50 | | | 28.92-39.20 | 34.1 ± 18.1 |
| **Negative** | 4 | | | 37.01-62.99 | 50.0 ± 8.2 |
| **PR expression** | | .004 | 8.937 | | |
| **Positive** | 40 | | | 25.71-36.69 | 31.2 ± 17.2 |
| **Negative** | 14 | | | 37.75-55.82 | 46.8 ± 15.6 |
| **Intrinsic subtypes** | | .033 | 3.157 | | |
| **ER+, PR+, HER2−** | 37 | | | 25.5-37.09 | 31.3 ± 17.4 |
| **ER+, PR+/−, HER2+/−** | 9 | | | 29.80-57.98 | 43.9 ± 18.3 |
| **HER2+ enriched** | 3 | | | 41.61-62.39 | 30.0 ± 17.3 |
| **Triple-negative BC** | 5 | | | 30.3-40.15 | 52.0 ± 8.4 |

**Table 4.** Multivariable linear regression analysis for assessing the predictors of Ki-67 expression.

| Predictors | 95% confidence interval | P-value | t-value | Standardized coefficients (Beta) | Standard error | Unstandardized coefficients (B) |
|---|---|---|---|---|---|---|
| **Age (years)** | -2.985 to 10.121 | .279 | 1.096 | 0.138 | 3.256 | 3.568 |
| **Tumor stage** | -1.933 to 8.590 | .210 | 1.272 | 0.172 | 2.617 | 3.328 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Estrogen receptor (ER) status** | -28.293 to 11.057 | .383 | -0.882 | -0.111 | 9.774 | -8.618 |
| **Progesterone receptor (PR) status** | 5.693 to 37.397 | .042 | 2.589 | 0.457 | 9.117 | 19.045 |
| **Intrinsic breast cancer subtype** | 3.397 to 16.503 | .032 | 3.056 | 0.373 | 3.256 | 9.950 |

What this investigation set out to achieve, first and foremost, was an examination of the interplay between the Ki-67 proliferation index and standard clinical-pathological variables in a cohort of male BC patients managed within a resource-constrained environment. The most striking pattern to emerge from the data was the marked upregulation of Ki-67 within those disease subsets long understood to signal aggressive tumor biology—specifically, TNBC and tumors lacking PR expression.

Notwithstanding the persistent lack of a universally endorsed Ki-67 threshold for prognostic assessment across malignancies, this biomarker remains highly promising. The readout, obtained by MIB-1 antibody detection, quantifies the proliferative activity within neoplastic cells of a given tumor; as tumor aggressiveness increases, so too does the measured proliferation. Even among studies that first define specific cut-off values before investigating links between Ki-67 and other prognostic features, the published record repeatedly affirms positive associations between Ki-67 expression and conventional clinical-pathological metrics, as well as diverse survival analyses—overall survival, event-free survival, progression-free survival, and beyond [19, 31-33].

Regarding the association between Ki-67 expression and HRs, a striking majority of tumors in the present series were ER-positive, a finding that aligns with earlier studies [34-36]. Prior work has established that MBCs, together with BCs occurring in postmenopausal women, generally demonstrate more robust ER expression than what is detected in males unaffected by BC [37]. Although our dataset failed to reveal a meaningful association between ER expression and elevated Ki-67 levels, the subgroup of cases lacking ER expression showed higher mean Ki-67 values than tumors retaining ER positivity. In the work published by Kilickap *et al*. [38], a link between elevated Ki-67 expression and absent ER staining was documented, a combination known to herald poor outcomes in both FBC and MBC. Individuals with ER-positive BC can usually expect to derive clinical benefit from hormonal therapeutic agents (HTs), including tamoxifen and the aromatase inhibitors anastrozole and letrozole [39, 40], a scenario that stands in direct opposition to ER-negative BC cases, which realize no advantage from estrogen inhibition—thereby permitting unchecked disease progression and worsening prognosis [41, 42]. MBCs that fail to express PR, however, and particularly those that additionally lack both ER and HER2, typically follow a far more aggressive trajectory, and the bulk of such tumors ultimately prove to be TNBCs [43, 44]. Those BCs marked by PR-negative status regularly confer considerably curtailed survival that far outstrips the impact attributable to ER-negative status alone [14], and correspondingly, these tumors demonstrate high Ki-67 expression [45]. Data derived from the current study established a significant correlation between PR-negative status and robust Ki-67 expression, suggesting tumors of greater aggressiveness and swifter growth. This observation dovetails with patterns documented by André *et al*. [46]. The same research group, André *et al*. [46], further noted that the combination of PR negativity and male sex in BC was associated with both high Ki-67 expression and BRCA2 gene alterations. Regarding the prognostic significance of PR negativity, accumulating evidence indicates that PR-negative MBCs generally have a worse clinical course, with shorter survival and accelerated disease progression, compared with PR-negative FBCs [16, 47, 48]. This reinforces the premise that the absence of PR expression in MBC provides particularly meaningful information for predicting clinical trajectories in male patients, paralleling its utility in female disease.

A well-established body of evidence confirms that TNBC harbors elevated Ki-67 expression in both male and female forms of the disease. The underlying rationale is that TNBC is closely linked to a high rate of progression, a propensity for metastasis, and resistance to chemotherapeutic agents—characteristics that find expression, whether directly or indirectly, through accelerated tumor cell proliferation. Within the present study, the association between high Ki-67 expression and the TNBC subtype was statistically significant. This mirrors the results published by Arafah *et al*. [49], who demonstrated statistically significant Ki-67 expression in the TNBC subgroup. Similarly, an investigation by Hashmi *et al*. [50] documented that the Ki-67 labeling index reached its peak in TNBCs compared with other intrinsic subtypes. Abubakr *et al*. [51] likewise reported a significant association between elevated Ki-67 expression and TNBC in a study population including both sexes. When weighing the accumulated evidence, all investigations revealing a positive correlation between Ki-67 expression

and the TNBC intrinsic BC subtype converge on a shared conclusion. This BC subtype is often associated with higher-grade lesions, suggesting that Ki-67 expression may be a valuable surrogate biomarker for identifying high-risk subsets within the broader BC patient population.

A survey of the literature confirms that the HER2-enriched (HER2-E) BC subtype is associated with adverse clinical outcomes even when the disease is detected at a localized stage (stages I and II) [21, 52, 53], and it likewise correlates with shorter progression-free survival in patients managed with HTs [54]. Tumors classified as HER2-E BCs typically manifest a high Ki-67 proliferation index, a feature consistent with aggressive clinical demeanor, brisk growth, and, by extension, a less favorable prognosis [55-57]. The present series yielded a mean absolute Ki-67 expression value for the HER2-E subset that was markedly higher than those of the remaining BC subtypes, TNBC excepted—an outcome that echoes reports from other centers [55, 56]. It should be noted, however, that one study found that Ki-67 expression levels among patients with HER2-E BC were influenced by clinical context, with menopausal status emerging as a notable modifier. That particular analysis observed that women in the postmenopausal period faced greater odds of harboring HER2-E disease relative to women who were still premenopausal [58]. Adding further complexity, BRCA1-mutant BC cases exhibit a stronger predilection for the TNBC phenotype than for luminal BC categories [59]. Collectively, these strands of evidence highlight the necessity of embedding Ki-67 expression interpretation within the broader clinical picture—factoring in hormonal expression patterns, menopausal status, and intrinsic subtype identity.

The present investigation found no link between tumor stage and elevated Ki-67 expression. This result aligns with observations reported by Erices-Leclercq *et al*. [31] and Wang-Rodriguez *et al*. [33], who found that advanced-stage disease did not correlate with elevated Ki-67 levels. A separate systematic review with meta-analysis likewise concluded that Ki-67 expression and tumor stage were not associated when examined specifically among male BC patients [60]. In contrast, the work of André *et al*. [46] reported a positive association, with higher-stage MBC tumors associated with greater Ki-67 expression. Heterogeneity in sociodemographic indicators—such as disparities in household income and educational attainment across different study populations—likely fuels the observed inconsistencies in disease awareness and the propensity to pursue timely medical evaluation [61, 62]. Such factors facilitate earlier detection of conditions like BC, an issue of particular relevance among male patients who characteristically postpone seeking clinical attention; the downstream consequence is that the disease is frequently uncovered only after it has reached an advanced stage.

Breast cancer subtypes expressing ER+, PR+, and HER2− are known to pursue a more indolent growth trajectory relative to their ER+, PR+/−, and HER2+/− counterparts; these tumors have also been documented to exhibit lower Ki-67 expression compared with the ER+, PR+/−, and HER2+/− BC category, a difference that renders the latter group's prognosis less favorable than that associated with ER+, PR+, and HER2− BCs [63]. In our dataset, the ER+, PR+/−, and HER2+/− subtypes similarly showed significantly elevated Ki-67 expression compared with the ER+, PR+, and HER2− cases. Cheang *et al*. [56] put forward the notion that Ki-67 expression measurements could serve to distinguish ER+, PR+, and HER2− disease from ER+, PR+/−, and HER2+/− BC; their analysis revealed that the former typically registered Ki-67 levels below 14%, whereas the latter group exhibited Ki-67 expression at or above the 14% mark. Consistent with this pattern, Inic *et al*. [64] documented that high Ki-67 expression was associated with ER+, PR+/−, HER2+/− status, LNI, and advanced-stage presentation.

To the best of our knowledge, this is the first study in Uganda to systematically characterize intrinsic BC subtypes in a male patient population. Moreover, it is the sole Ugandan investigation to date to have shed light on the relationship between a recognized prognostic proliferation marker (Ki-67) and standard clinicopathological parameters in MBC. The work was not without methodological shortcomings, however. Chief among these was the unavailability of longitudinal follow-up data, which precluded any meaningful exploration of how Ki-67 expression might relate to patient survival outcomes. Compounding this, the disease's intrinsic rarity meant that the sample size remained limited, inevitably constraining the robustness of the inferences that could be drawn—including the curtailed generalizability of the findings and the inherent selection bias introduced by the hospital-centric nature of the data source. Additional limitations encompassed potential biases stemming from incomplete records, as tumor stage and tumor size were absent for a considerable proportion of cases, as well as the unavoidable reliance on convenience sampling. These issues, rooted in the retrospective study design and the well-recognized data quality deficiencies that plague LMICs, could not be circumvented.

**Conclusion**

The present study demonstrates that ER expression characterizes the vast majority of MBCs, with the ER+, PR+, HER2− (luminal A) subtype emerging as the predominant intrinsic subtype. High Ki-67 expression was associated with PR-negative status and the TNBC intrinsic subtype. These observations underscore the value of Ki-67 expression in gauging the aggressive potential of MBC, as defined by the cut-off threshold applied in this analysis.

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Written informed consent was obtained from the patients, and a copy has been retained for review by the journal's Editor-in-Chief.

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