

# Determining the Optimal Ki-67 Cutoff Point in Malaysian Patients With Breast Cancer.

CV Song<sup>1</sup>, CH van Gils<sup>1</sup>, CH Yip<sup>2</sup>, R Pathmanathan<sup>2</sup>, M Md Yusof<sup>2</sup>, MM Abdullah<sup>2</sup>, YC Foo<sup>2</sup>, BK Yap<sup>2</sup>, N Bhoo-Pathy<sup>3</sup>

1. UMC Utrecht, Utrecht, The Netherlands
2. Subang Jaya Medica Centre, Selangor, Malaysia
3. Universiti Malaya, Kuala Lumpur, Malaysia

**Introduction:** Ki-67 is a prognostic biomarker for breast cancer. The optimal cutoff to differentiate low Ki-67 from high Ki-67 in clinical decision making is unclear. We investigated the optimal cutoff value for dichotomising Ki-67.

**Materials and methods:** Data from a hospital-based breast cancer registry in Malaysia was used, where women newly-diagnosed with stage I to stage III breast cancer between 2014 and 2016 were included. Patients were divided into low Ki-67 vs. high Ki-67 groups using different Ki-67 cut-off values (10%, 15%, 20%, 25%, 30%). All-cause mortality between the groups were compared using Cox regression, including age, tumor size, number of positive lymph nodes, estrogen receptor expression and human epidermal growth factor receptor 2 expression. Univariable ROC curve analysis and Youden's Index were used to determine the optimal cutoff value in predicting mortality within five years.

**Results:** We included 912 patients. Median age was 51 years, and a vast majority of patients were Chinese (87.5%). Patients most commonly presented with stage I disease (39.7%), followed by stage II disease (36.1%). Over a median follow-up of 86 months, 88 deaths were observed. The median Ki-67 was 10%. Patients with higher Ki-67 had worse survival; hazard ratios ranged from 1.69 (95% CI: 1.01 – 2.82) at a cutoff of 10%, to 1.96 (95% CI: 1.16 – 3.29) at cutoff of 30%. ROC curve analysis, Youden's Index indicated that a Ki-67 value of 16.5% was optimum. The corresponding hazard ratio was 1.72 (95% CI: 1.06 – 2.78).

**Conclusion:** In this cohort of multiethnic Asian patients, Ki67 appeared to be an independent prognostic factor of poorer survival. The cutoff point derived from the present analysis (16.5%) supports the use of 15% as the optimal cut-off value for Ki67 in Asian populations.

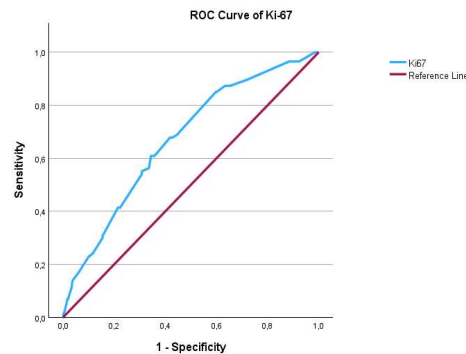
**Limitation:** There is lack of standardized Ki-67 measurement across institutions. Hence, our results may not be applicable to other institutions.

### Summary:

**-Ki-67 is an important prognostic factor for breast cancer patients.**

**-Higher Ki-67 percentage is associated with poorer survival.**

**-Our findings suggest a cut-off of 15% is optimal for differentiating low/ high Ki-67.**



Ki-67 Cutoff	Hazard ratio* (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
<b>10%</b>	1.69 (1.01 – 2.82)	70.11 (59.35 – 79.46)	54.30 (50.83 – 57.74)	13.93 (12.16 – 15.91)	94.51 (92.54 – 95.99)
<b>15%</b>	1.67 (1.03 – 2.71)	60.92 (49.87 – 71.21)	64.24 (60.86 – 67.52)	15.23 (12.92 – 17.87)	93.97 (92.27 – 95.32)
<b>20%</b>	1.47 (0.93 – 2.34)	41.38 (30.92 – 52.45)	77.70 (74.70 – 80.50)	16.36 (12.87 – 20.57)	92.63 (91.30 – 93.77)
<b>25%</b>	1.65 (1.02 – 2.68)	31.03 (21.55 – 41.86)	84.36 (81.70 – 86.78)	17.31 (12.84 – 22.92)	92.06 (90.95 – 93.05)
<b>30%</b>	1.96 (1.16 – 3.29)	24.14 (15.60 – 34.50)	88.36 (85.98 – 90.47)	17.95 (12.60 – 24.93)	91.70 (90.73 – 92.57)

\*adjusted for age, size, lymph nodes, estrogen receptor and HER2 receptor