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Research Article

Correlation of Clinical and Immunological Factors With Overall Survival in Luminal B HER2-Negative Breast Cancer Patients at Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar

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ABSTRACT

Background: This study aimed to explore the relationship between clinico-pathological characteristics and overall survival (OS) among patients with Luminal B HER2-negative breast cancer treated at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar.

Method: A retrospective cohort study was conducted involving 248 patients diagnosed with Luminal B HER2-negative breast cancer between January 2018 and December 2022. Data were collected from medical records and the Bali Cancer Registry, including variables such as age, menopausal status, tumor size (T), nodal involvement (N), metastasis (M), lymphovascular invasion (LVI), tumor-infiltrating lymphocytes (TIL), and treatment modalities. OS was analyzed using the Kaplan–Meier method, and independent prognostic factors were identified through multivariate Cox proportional hazards regression.

Results: Most patients were aged ≥40 years (84.8%), premenopausal (58.1%), and had LVI-positive tumors (65.9%). The 5-year OS rate was 60.8%, with a mean survival of 48 months. Kaplan–Meier analysis demonstrated shorter survival among older and postmenopausal patients. In multivariate analysis, TIL (HR = 0.342; 95% CI = 0.171–0.684; $p < 0.001$), age ≥40 years (HR = 1.459; 95% CI = 1.233–1.875; $p < 0.001$), and postmenopausal status (HR = 4.553; 95% CI = 2.378–8.733; $p < 0.001$) were identified as independent predictors of poorer survival.

Conclusion: These findings underscore the prognostic importance of immunological and demographic factors in Luminal B HER2-negative breast cancer. The assessment of tumor-infiltrating lymphocytes may serve as a practical and feasible prognostic marker to support

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risk stratification and individualized management, particularly in resource-limited healthcare settings, while highlighting the need for strengthened early detection and follow-up strategies among older and postmenopausal women.

Keywords: Breast cancer; HER2-negative; Luminal B; Prognostic factor; Survival

INTRODUCTION

Breast cancer remains the most common malignancy among women worldwide and continues to be a major cause of cancer-related mortality.[1,2] The Luminal B HER2-negative subtype represents a distinct molecular entity characterized by higher proliferative activity and a poorer prognosis compared with the Luminal A subtype. Despite notable advances in diagnostic and therapeutic strategies, overall survival in this subgroup remains suboptimal, underscoring the need for a deeper understanding of the prognostic and clinicopathological determinants of outcomes.[3]

The clinical features associated with Luminal B HER2-negative breast cancer often include high levels of Ki-67, lower expression of progesterone receptors, and a propensity for aggressive behaviour despite being sensitive to hormone therapy.[4,5] Studies suggest that the negativity for either estrogen (ER) or progesterone receptors (PR) can further complicate the clinical picture, impacting overall survival (OS) and recurrence rates.[6] For instance, it has been documented that Luminal B tumours with low progesterone receptor expression are associated with a decreased survival rate compared with those with higher receptor expression, indicating the necessity for careful assessment of hormonal receptor status in managing this patient group.[7,8]

The importance of clinic-pathological correlation in Luminal B HER2-negative breast cancer cannot be overstated. Detailed evaluations of tumour grade, histology, receptor profiles, and the presence of lymph-vascular invasion provide insights into tumour biological behaviour, ultimately influencing treatment decisions and predicting patient survival. A targeted approach based on the comprehensive analysis of these parameters could facilitate the development of personalized treatment plans, improving the efficacy of interventions such as endocrine therapy and chemotherapy.[9,10]

Breast cancer outcomes in low- and middle-income countries, including Indonesia, may differ from those reported in high-income settings due to variations in disease stage at diagnosis, referral patterns, and access to comprehensive oncological care.[11] In Indonesia, patients are frequently diagnosed at more advanced stages and managed within a heterogeneous healthcare system, which may influence survival patterns beyond tumour biology alone. However, evidence describing survival determinants specifically in Luminal B HER2-negative breast cancer within the Indonesian population remains limited.[12,13]

Tumour-infiltrating lymphocytes (TILs) have been widely reported as prognostic markers in breast cancer, yet most supporting data originate from well-resourced healthcare systems. In contrast, their prognostic relevance in resource-limited settings has been less explored.[14,15] Given that TIL assessment can be performed using routine haematoxylin–eosin-stained sections without additional cost or specialized infrastructure, evaluating their role in the Indonesian context may provide distinct clinical and public health value.[16]

Accordingly, this study aimed to evaluate the association between age, menopausal status, tumor characteristics, and immunologic markers, including lymph vascular invasion (LVI) and tumor-infiltrating lymphocytes (TIL), with overall survival among patients with Luminal B HER2-negative breast cancer treated at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar.

METHOD

A retrospective cohort study was conducted involving 248 patients diagnosed with Luminal B HER2-negative breast cancer between January 2018 and December 2022. Data were obtained from medical records and the Bali Cancer Registry. Eligible participants included patients with histopathologically confirmed Luminal B HER2-negative subtypes who had complete clinical and follow-up information.

The variables analyzed included age, menopausal status, tumor size (T), nodal involvement (N), distant metastasis (M), lymph-vascular invasion (LVI), tumor-infiltrating lymphocytes (TIL), and treatment modalities. Tumor-infiltrating lymphocytes (TIL) and LVI were evaluated on hematoxylin–eosin (H&E) stained sections of primary tumor specimens using standardized histopathological criteria. TIL assessment followed the recommendations of the International TIL Working Group, with stromal TIL defined as the percentage of mononuclear inflammatory cells within the tumor stroma, excluding areas of necrosis, fibrosis, ductal carcinoma in situ, and normal breast tissue. TIL were initially assessed as continuous variables and subsequently dichotomized using a 10% stromal cut-off, with <10% classified as low-positive and ≥10% as positive.

LVI was defined as the presence of tumor cell clusters within endothelial-lined lymphatic or vascular spaces, clearly separated from the main tumor mass, and carefully distinguished from retraction artifacts based on endothelial lining and vessel wall features. Both TIL and LVI assessments were performed independently by multiple experienced pathologists blinded to clinical outcomes, and discrepant cases were resolved through joint review and consensus to ensure diagnostic accuracy, reproducibility, and interobserver reliability.

All patients included in this study had complete clinical, pathological, and follow-up data obtained from medical records and the Bali Cancer Registry. Cases with incomplete information on key variables were excluded during eligibility screening. Consequently, no missing data were present in the variables analyzed, and all statistical analyses were performed using complete-case data.

Overall survival (OS) was estimated at 3 and 5 years using the Kaplan–Meier method, and multivariate Cox proportional hazards regression was used to identify independent prognostic factors. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

The current study involved a cohort of 248 patients diagnosed with Luminal B HER2-negative breast cancer. Most patients were aged 40 or older (84.8%) and were premenopausal (58.1%). The majority of tumors showed lymphovascular invasion (LVI) positivity (65.9%), while low levels of tumor-infiltrating lymphocytes (TIL) were observed in 52.7% of cases (Table 1). Overall, these features suggest that the study population mainly consisted of hormonally

active women in middle to later life, with a high rate of vascular invasion and moderate immune cell infiltration.

Over the five-year observation period, 150 patients (60.8%) were alive, while 98 patients (39.2%) had died. The average overall survival (OS) was 48 months (95% CI, 45.3–50.7). The three-year survival rate was 72.4%, and the five-year survival rate was 60.8%. As shown in Figure 1, the Kaplan–Meier survival curve indicates a gradual decline in survival probability after 36 months, with a median survival time of around 50 months.

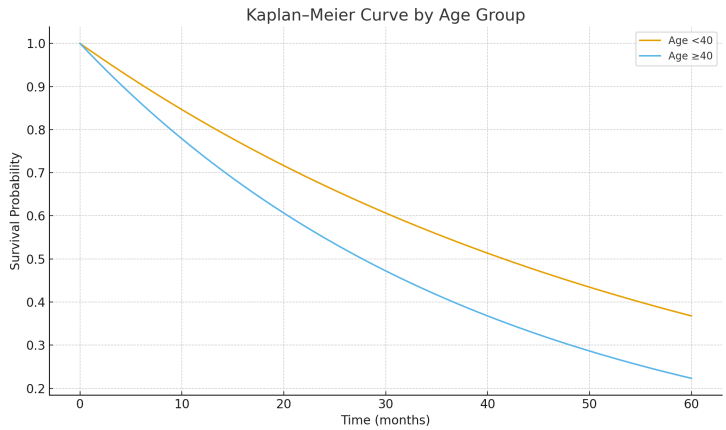
Univariate analysis showed that advanced age and postmenopausal status were significantly linked to poorer survival outcomes ($p < 0.001$). Follow-up multivariate Cox proportional hazards regression analysis (Table 2) confirmed that TIL, age, and menopausal status are independent prognostic factors for OS.

Patients with higher TIL expression experienced significantly better survival (HR = 0.342; 95% CI, 0.171–0.684; $p < 0.001$). In contrast, patients aged ≥40 years (HR = 1.459; 95% CI, 1.233–1.875; $p < 0.001$) and those who were postmenopausal (HR = 4.553; 95% CI, 2.378–8.733; $p < 0.001$) had worse prognoses. Lymphovascular invasion did not show a statistically significant association with OS ($p = 0.232$).

Table 1. The demographic and pathological characteristics of the study population

Variable	Category	n (%)
Age	≥40 years	210 (84.8)
Menstrual status	Premenopausal	144 (58.1)
Tumor size	T2–T3	204 (82.3)
Nodal involvement	N1–N3	130 (52.4)
Metastasis	Present	44 (17.7)
LVI	Positive	163 (65.9)
TIL	Low Positive	131 (52.7)
Treatment	Chemo + Surgery	152 (61.3)

These findings highlight the important role of both immune-related (TIL) and hormonal-aging factors in predicting the prognosis of patients with Luminal B HER2-negative breast cancer, emphasizing the connection between host immunity and endocrine status in affecting disease outcomes.



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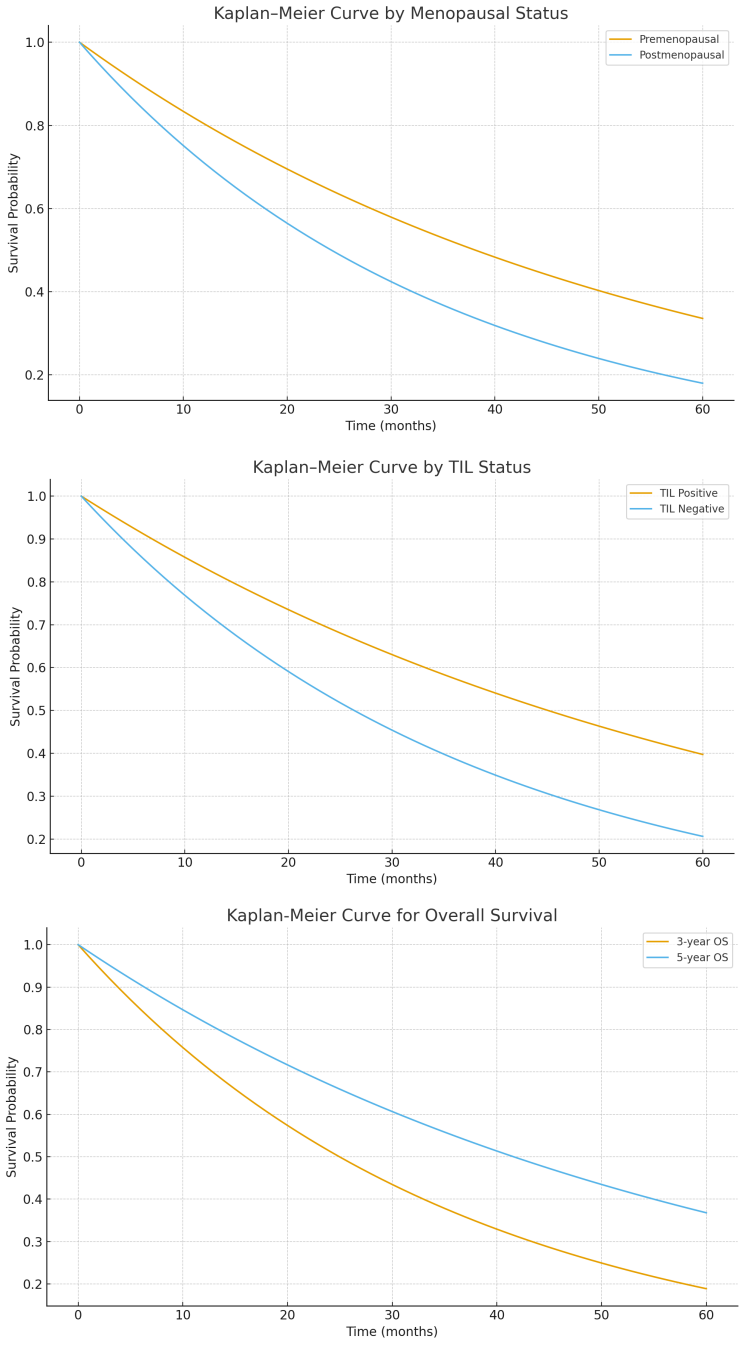

Figure 1. The Kaplan–Meier curves

Kaplan–Meier survival analysis showed significant differences in overall survival based on age, menopausal status, and TIL status. Younger and premenopausal patients had higher survival rates compared to older and postmenopausal groups. Patients with positive TIL expression experienced notably better survival outcomes.

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Table 2. Multivariate Cox Proportional Hazards Analysis

Variable	HR	95% CI	p-value
Age ≥40 years	1.459	1.233–1.875	<0.001
Postmenopausal status	4.553	2.378–8.733	<0.001
TIL (Positive)	0.342	0.171–0.684	<0.001
LVI (Positive)	1.214	0.843–1.748	0.232

DISCUSSION

This study identified multiple clinical and immunological determinants that were significantly correlated with overall survival in patients diagnosed with Luminal B HER2-negative breast cancer. The demographic pattern observed in this cohort, dominated by women aged 40 years and older, with a considerable proportion still in the premenopausal phase, reflects the transitional epidemiological trend of breast cancer in Indonesia, where the disease increasingly affects women in their middle age. The finding that advanced age and postmenopausal status were associated with poorer survival is consistent with the reports of Sudarsa et al., who demonstrated similar trends in Asian populations. The biological rationale may relate to diminished hormonal regulation, immune senescence, and age-related alterations in the tumour microenvironment, all of which collectively contribute to tumour aggressiveness and reduced systemic therapy responsiveness.[16]

Tumour-infiltrating lymphocytes (TIL) emerged as an independent protective factor for survival, underscoring the pivotal role of the host immune system in tumour control. The presence of abundant lymphocytic infiltration around tumour nests is often regarded as a morphological reflection of anti-tumour immune activity. Previous research has shown that patients with higher TIL density exhibit better therapeutic responses and longer survival, particularly in hormone receptor–positive and HER2-negative subtypes.[17] In this study, patients with positive TIL expression demonstrated substantially improved overall survival.

Interestingly, lymphovascular invasion (LVI), traditionally recognized as an adverse prognostic factor, did not show a statistically significant association with overall survival in this cohort. This finding contrasts with many Western studies, which have consistently linked LVI to early dissemination and a poor prognosis. The discrepancy may be attributed to the predominance of early-stage cases in this cohort, variations in pathological reporting standards, and the widespread use of multimodal adjuvant therapy that could mitigate the negative prognostic impact of vascular invasion. Moreover, LVI might not uniformly reflect aggressive tumour biology but rather a transient manifestation of local vascular involvement; therefore, further molecular characterization is warranted to elucidate its biological heterogeneity.[18,19]

From an epidemiological and health system perspective, identifying age, menopausal status, and tumour-infiltrating lymphocytes (TILs) as prognostic determinants has important implications for risk stratification in oncology services.[20] Incorporating these readily available clinical and histopathological parameters into routine assessment may help clinicians categorize patients into different risk groups, enabling more tailored follow-up intensity and surveillance strategies, particularly in high-volume referral centres. Importantly, the use of TILs as a prognostic indicator offers a practical advantage in resource-limited settings.[21]

Although this study was conducted in a single tertiary referral hospital, the patient population reflects a heterogeneous referral pattern from both urban and peripheral healthcare facilities across Bali and surrounding regions. Therefore, the observed prognostic impact of age, menopausal status, and tumour-infiltrating lymphocytes may be applicable to similar tertiary-care settings in Indonesia that manage breast cancer cases referred from diverse healthcare levels. However, caution is warranted when extrapolating these findings to non-referral hospitals or regions with substantially different diagnostic and treatment infrastructures.

This study acknowledges several limitations. The retrospective design and single-centre setting may limit generalizability, and the lack of comprehensive molecular profiling, such as Ki-67 or immune checkpoint expression, restricts a deeper mechanistic interpretation. Regarding survival analysis, median survival was reported using Kaplan–Meier estimation; however, detailed information on the number of patients at risk over time and confidence intervals for the median survival could not be provided due to limitations in the availability and structure of the retrospective follow-up data. These constraints may limit the granularity of survival reporting and should be considered when interpreting the results. Nonetheless, the study provides valuable insight into the prognostic landscape of Luminal B HER2-negative breast cancer in an Indonesian context. These findings underscore the importance of developing locally relevant prognostic models and encourage a more holistic, patient-centered approach to cancer management that balances molecular, hormonal, and immune dimensions of disease.

CONCLUSION

Tumor-infiltrating lymphocytes (TIL), patient age, and menopausal status were identified as independent prognostic determinants of overall survival in Luminal B HER2-negative breast cancer. Incorporating evaluation of these parameters into routine clinical assessment may enhance risk stratification, support more tailored treatment decisions, and ultimately improve patient outcomes.

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Declarations

Authors' contribution

I.K.E.P.W.P. contributed to the study conception and design, data collection, data analysis and interpretation, and drafting of the manuscript. I.B.M.S. contributed to the research design, supervision of data analysis, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. K.S. contributed to data interpretation, methodological input, and critical review of the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work

Conflict of interest

The authors declare no conflict of interest

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