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Clinicopathological Characteristics Associated with Survival in Pregnancy-Associated Breast Cancer at Ngoerah Hospital

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ABSTRACT

Background: Pregnancy-associated breast cancer (PABC) is a rare but complex condition with generally poorer prognosis compared to non-PABC. Delayed diagnosis and aggressive tumor characteristics contribute to unfavorable outcomes. ***Objective:*** This study aimed to analyze the association between clinicopathological characteristics and overall survival in patients with PABC at Ngoerah Hospital. ***Methods:*** A retrospective cohort study was conducted using secondary data from medical records and the Bali Cancer Registry. Patients diagnosed with PABC between January 2018 and December 2023 were included. Variables analyzed included age at diagnosis, tumor size, nodal status, metastasis, stage, histological grade, lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes (TIL). Survival analysis was performed using the Kaplan–Meier method and Cox proportional hazards regression. ***Results:*** A total of 58 patients were included. Most patients were aged <40 years (63.8%) and presented with advanced disease (Stage III–IV: 72.4%). The 5-year overall survival rate was 56.9%. The higher stage was significantly associated with poorer survival ($p<0.01$). Other variables, including age, tumor size, nodal status, and metastasis, showed trends toward worse outcomes but were not statistically significant. ***Conclusion:*** Advanced stage is a significant prognostic factor for survival in PABC patients. Early detection remains crucial to improving outcomes.

Keywords: pregnancy-associated breast cancer; survival; clinicopathological characteristics; prognosis

INTRODUCTION

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy, within the first year postpartum, or during lactation. Although relatively rare, PABC represents a significant clinical challenge due to its impact on both maternal and fetal outcomes.

The incidence of PABC ranges from 15 to 35 cases per 100,000 pregnancies and is increasing as more women delay childbirth to older ages. Diagnosis is often delayed due to physiological breast changes during pregnancy, leading to more advanced disease at presentation, including larger tumor size, lymph node involvement, and distant metastasis (Albrektsen, Heuch, Hansen, & Kvåle, 2005).

Biologically, PABC tends to exhibit more aggressive features, including higher histological grade and increased prevalence of hormone receptor-negative subtypes. Additionally, hormonal changes and immunological modulation during pregnancy may contribute to tumor progression (Stensheim, Møller, van Dijk, & Fosså, 2009).

Despite increasing recognition, the prognostic factors influencing survival in PABC remain controversial. Therefore, this study aims to evaluate clinicopathological factors associated with survival in PABC patients treated at Ngoerah Hospital.

METHODS

This study was conducted using an observational analytic design with a retrospective cohort approach. Secondary data were obtained from medical records and the Bali Cancer Registry of patients diagnosed with pregnancy-associated breast cancer (PABC) who received treatment at Ngoerah Hospital, Denpasar, Indonesia, between January 1, 2018, and December 31, 2023.

The study population consisted of all patients diagnosed with PABC, defined as breast cancer identified during pregnancy, within the first year

postpartum, or during lactation. Eligible subjects were those with histopathologically confirmed diagnoses and complete clinical data. Patients with a history of other malignancies or whose mortality was attributed to non-cancer-related causes were excluded from the analysis.

Sampling was performed using a consecutive sampling technique, in which all eligible patients meeting the inclusion and exclusion criteria during the study period were included until the required sample size was achieved. A minimum sample size of 51 patients was calculated based on survival analysis requirements, and a total of 58 patients were ultimately included in this study.

Data collected included clinicopathological variables such as age at diagnosis, tumor size, lymph node involvement, presence of distant metastasis, tumor stage based on the AJCC TNM classification, histological grade, lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes (TIL). The primary outcome measured was overall survival, defined as the duration from the time of diagnosis to death or last follow-up within a 5-year observation period.

Data processing was carried out through several stages, including data verification, coding, entry into a computerized database, and data cleaning to ensure completeness and accuracy. Statistical analysis was performed using SPSS software. Descriptive statistics were used to summarize baseline characteristics. Survival analysis was conducted using the Kaplan–Meier method to estimate survival probabilities, while prognostic factors associated with survival were analyzed using Cox proportional hazards regression. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 58 patients diagnosed with pregnancy-associated breast cancer (PABC) who met the inclusion and exclusion criteria were included in this study. The majority of patients were younger than 40 years, accounting for 63.8% of cases, while 36.2% were older than 40 years.

TABLE 1: Subject Characteristics.

Variable	n=58
Age, n (%)	
< 40 years	37 (63,8)
≥ 40 years	21 (36,2)
Stage	
I	0 (0,0)
II	16 (27,6)
III	24 (41,4)
IV	18 (31,0)
Tumor Size, n (%)	
T1	0 (0,0)
T2	14 (24,1)
T3	14 (24,1)
T4	30 (51,7)
Lymph Node(s), n (%)	
N0	12 (20,7)
N1	29 (50,0)
N2	14 (24,1)
N3	3 (5,2)
Distant Metastasis, n (%)	
Negative	40 (69,0)
Positive	18 (31,0)
Histopathologic Grade, n (%)	
Grade I	4 (6,9)
Grade II	23 (39,7)
Grade III	28 (48,3)
Missing	3 (5,2)
Lymphovascular Invasion (LVI), n (%)	
Negative	26 (44,8)
Positive	19 (32,8)
Missing	13 (22,4)
Tumor Infiltrating Lymphocyte (TIL), n (%)	
Negative	18 (31,0)
Positive	27 (46,6)
Missing	13 (22,4)
5 Years Survival, n (%)	
Survived	33 (56,9)
Not Survived	25 (43,1)

In terms of disease characteristics, most patients presented with advanced-stage disease. Stage III was the most common (41.4%), followed by Stage IV (31.0%) and Stage II (27.6%), while no patients were diagnosed at Stage I. Tumor size distribution showed that more than half of the patients had large tumors classified as T4 (51.7%), while T2 and T3 tumors were each observed in 24.1% of patients, and no cases of T1 tumors were reported.

Regarding lymph node involvement, the majority of patients had nodal metastasis, with N1 being the most frequent (50.0%), followed by N2 (24.1%) and N3 (5.2%), whereas only 20.7% had no nodal involvement (N0). Distant metastasis was identified in 31.0% of patients, while the remaining 69.0% showed no evidence of metastasis.

Histopathological evaluation revealed that most tumors were high-grade, with Grade III observed in 48.3% of patients, followed by Grade II in 39.7%, and Grade I in only 6.9%. Lymphovascular invasion (LVI) was present in 32.8% of cases and absent in 44.8%, while the remaining cases had no available data. Tumor-infiltrating lymphocytes (TIL) were positive in 46.6% of patients and negative in 31.0%, with missing data in a proportion of cases.

During the 5-year follow-up period, 33 patients (56.9%) were alive, while 25 patients (43.1%) had died, indicating an overall survival rate of 56.9%. Analysis of survival based on age at diagnosis showed that patients younger than 40 years had a higher 5-year survival rate (62.2%) compared to those older

than 40 years (47.6%). However, this difference was not statistically significant (p>0.05).

Survival analysis based on tumor stage demonstrated a significant association between stage and overall survival. Patients with Stage II disease had the highest survival rate (75%), followed by Stage III (66.7%), while Stage IV patients had a markedly lower survival rate (27.8%). This difference was statistically significant (p<0.01).

Tumor size also showed a trend toward worse outcomes with increasing size. Patients with T2 and T3 tumors had survival rates of 57.1% and 71.4%, respectively, whereas patients with T4 tumors had a lower survival rate of 50%. However, this association was not statistically significant (p>0.05). Similarly, increasing lymph node involvement was associated with decreasing survival rates. Patients with N0 disease had a survival rate of 75.0%, while those with N1, N2, and N3 disease had survival rates of 55.2%, 50.0%, and 33.3%, respectively. Despite this trend, the association was not statistically significant (p>0.05).

Patients with distant metastasis had substantially lower survival rates compared to those without metastasis. Among patients with metastasis, the 5-year survival rate was approximately 27.8%, whereas patients without metastasis demonstrated considerably better outcomes. However, this difference did not reach statistical significance.

Overall, among all clinicopathological variables analyzed, only tumor stage demonstrated a statistically significant association with overall survival, while other factors showed trends but lacked sufficient statistical evidence.

DISCUSSION

This study evaluated the association between clinicopathological characteristics and overall survival in patients with pregnancy-associated breast cancer (PABC) treated at Ngoerah Hospital. The findings demonstrate that the majority of patients presented at a relatively young age and with advanced-stage disease, and that tumor stage was the only factor significantly associated with survival outcomes.

One of the most notable findings in this study is that most patients were younger than 40 years at the time of diagnosis. This is consistent with the epidemiological profile of PABC, which predominantly affects women of reproductive age. However, despite the generally younger age group, a substantial proportion of patients presented with advanced disease. This observation highlights a critical clinical issue, namely, delayed diagnosis. Physiological changes in the breast during pregnancy and lactation, such as increased glandular density, nodularity, and tenderness often obscure early tumor detection. As a result, malignancies are frequently identified only when they have reached a more advanced stage, contributing to poorer outcomes.

The predominance of advanced-stage disease in this cohort is particularly important. Most patients were diagnosed at Stage III and IV, with no cases detected at Stage I. This distribution reflects a systemic challenge in early detection of PABC and is in line with previous studies reporting delayed presentation in pregnant and postpartum patients. Importantly, tumor stage was found to be the only variable significantly associated with survival in this study. Patients with Stage IV disease had markedly lower survival compared to those with earlier stages, reinforcing the well-established role of stage as the most critical prognostic factor in breast cancer.

Although age at diagnosis did not show a statistically significant association with survival, an interesting trend was observed in which younger patients (<40 years) demonstrated better survival compared to older patients. This finding contrasts with some literature suggesting that younger age is associated with more aggressive tumor biology. One possible explanation is that younger patients may have better physiological reserve, allowing them to tolerate more aggressive treatments. Additionally, this finding may be influenced by the relatively small sample size, which limits statistical power.

Tumor size and nodal involvement also demonstrated a consistent trend toward worse survival with increasing severity, although these associations did not reach statistical significance. Patients with larger tumors (T4) and higher nodal burden (N2–N3) had lower survival rates compared to those with less advanced disease. These findings are biologically plausible, as larger tumor size and lymph node metastasis reflect greater tumor burden and increased likelihood of systemic dissemination. However, the lack of statistical significance suggests that these variables may be confounded by stage or that the study was underpowered to detect these associations independently.

Similarly, the presence of distant metastasis was associated with markedly reduced survival, although statistical significance was not achieved. Patients with metastasis had substantially lower survival rates compared to those without metastasis. This finding aligns with the natural history of breast cancer, where metastatic disease is associated with poor prognosis due to limited curative treatment options. The absence of statistical significance in this study may again be attributed to the limited sample size and variability in treatment approaches.

Histopathological characteristics, including tumor grade, lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes (TIL), were also evaluated. A high proportion of patients had Grade III tumors, indicating aggressive tumor biology. Although high-grade tumors are generally associated with poorer prognosis, this study did not demonstrate a statistically significant relationship between grade and survival. This may reflect the dominant influence of stage over other pathological factors in determining survival outcomes.

Lymphovascular invasion, which is considered a marker of tumor aggressiveness and metastatic potential, was present in approximately one-third of patients. While LVI-positive patients are generally expected to have worse outcomes, this study did not find a significant association with survival. Similarly, TIL status, which has been increasingly recognized as a prognostic and predictive biomarker in breast cancer, did not show a significant relationship with survival in this cohort. The variability and incomplete data in these variables may have contributed to these findings.

From a pathophysiological perspective, the aggressive nature of PABC may be influenced by several unique factors. The hormonal milieu during pregnancy, characterized by elevated levels of estrogen, progesterone, and growth factors, may promote tumor proliferation. In addition, the immunological changes associated with pregnancy, including relative immunosuppression, may allow tumor cells to evade immune surveillance. The postpartum involution process, which resembles wound healing and is associated with inflammation and extracellular matrix remodeling, has also been implicated in promoting tumor progression and metastasis.

Another important consideration is the complexity of treatment decision-making in PABC. Management must balance optimal oncological outcomes for the mother with safety considerations for the fetus. This often leads to modifications or delays in standard treatment protocols, which may adversely affect prognosis. For example, radiotherapy is typically deferred until after delivery, and certain systemic therapies are contraindicated during pregnancy. These limitations may contribute to suboptimal disease control in some patients.

This study has several limitations that should be acknowledged. First, the retrospective design introduces potential bias related to data completeness and accuracy. Second, the relatively small sample size limits the statistical power to detect significant associations for some variables. Third, the study was conducted at a single center, which may limit generalizability to other populations. Additionally, incomplete data for certain variables, such as LVI and TIL, may have influenced the results.

Despite these limitations, this study provides valuable insight into the clinicopathological characteristics and survival outcomes of PABC in a real-world clinical setting. The findings underscore the critical importance of early detection and prompt management to improve survival outcomes. Increased awareness among clinicians and patients regarding the possibility of breast cancer during pregnancy is essential to reduce diagnostic delays.
Future studies with larger, multicenter cohorts and prospective designs are needed to better elucidate the prognostic factors associated with PABC. Additionally, further research into the biological mechanisms underlying the aggressive behavior of PABC may provide opportunities for targeted therapeutic interventions.

CONCLUSIONS

This study demonstrates that pregnancy-associated breast cancer (PABC) at Ngoerah Hospital is predominantly diagnosed in younger women and is frequently identified at an advanced stage. The high proportion of patients presenting with Stage III and IV disease reflects the persistent challenge of delayed diagnosis in this population, likely due to physiological breast changes during pregnancy and lactation that obscure early detection.

Among the clinicopathological variables analyzed, tumor stage was identified as the only factor significantly associated with overall survival. Patients with advanced-stage disease exhibited substantially poorer survival outcomes, highlighting the critical role of early-stage detection in improving prognosis. Although other factors, including age at diagnosis, tumor size, lymph node involvement, metastasis, histological grade, lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes (TIL), demonstrated trends toward influencing survival, these associations were not statistically significant in this study. This suggests that while these variables may contribute to disease progression, their independent prognostic value may be limited or requires larger sample sizes to be clearly established.

The findings of this study reinforce the importance of early recognition and prompt diagnostic evaluation of breast abnormalities during pregnancy and the postpartum period. Increased clinical awareness and a lower threshold for further investigation, including imaging and biopsy when indicated, are essential to reduce diagnostic delay and prevent progression to advanced disease.

From a clinical perspective, management of PABC requires a multidisciplinary approach that carefully balances optimal oncologic treatment for the mother with the safety of the fetus. The complexity of treatment decisions may also contribute to variations in outcomes, emphasizing the need for individualized and timely therapeutic strategies.

In conclusion, advanced tumor stage remains the most important determinant of survival in patients with PABC. Efforts to improve early detection, optimize diagnostic pathways, and ensure appropriate multidisciplinary management are crucial to enhance survival outcomes in this patient population. Future studies with larger cohorts and prospective designs are needed to further clarify the role of additional prognostic factors and to guide the development of more effective management strategies for PABC.

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