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ORIGINAL ARTICLE

Platelet-Lymphocyte Ratio in Positive Sentinel Lymph Node in Early Breast Cancer

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ABSTRAK

Platelet berperanan dalam menggalakkan perkembangan tumor, manakala limfosit penting untuk pengawasan imun terhadap kanser, menunjukkan bahawa nisbah platelet kepada limfosit (PLR) berpotensi meramalkan tingkah laku tumor malignan. Kajian keratan rentas di satu pusat ini dijalankan untuk menilai hubungan antara PLR prapembedahan dan keputusan positif biopsi nodus limfa sentinel (SLNB) dalam kanser payudara awal. Objektif sekunder kajian ini adalah untuk menilai hubungan antara SLNB positif dengan ciri-ciri klinikopatologi. PLR prapembedahan dikira berdasarkan nisbah antara jumlah platelet mutlak dengan jumlah limfosit mutlak, menggunakan nilai ambang 127.1 yang ditentukan melalui ciri operasi penerima (Luas di bawah lengkung = 0.53). Analisis statistik dilakukan menggunakan ujian Chi-Square Pearson. Dalam kalangan 271 wanita dengan kanser payudara peringkat awal yang menjalani SLNB, sebanyak 17.7% (n = 48) mempunyai SLNB positif. Tiada korelasi yang signifikan ditemui antara PLR dan SLNB positif (p = 0.193). Namun begitu, PLR yang tinggi menunjukkan hubungan signifikan dengan etnik Cina (OR 2.524, 95% CI 1.05-6.069, p = 0.039). Kesimpulannya, PLR prapembedahan tidak dapat meramalkan keputusan positif SLNB dalam kanser payudara peringkat awal dan mungkin tidak sesuai digunakan sebagai parameter prapembedahan untuk menilai metastasis nodus limfa sentinel. Kajian lanjut diperlukan untuk mengkaji penanda ramalan alternatif.

Kata kunci: *Biopsi nodus limfa sentinel; kanser payudara; limfosit; platelet*

ABSTRACT

Platelets promote tumour progression, while lymphocytes are critical for cancer immune surveillance, suggesting that the platelet-to-lymphocyte ratio (PLR) may reflect malignant tumour behaviour. This is a single-centre, cross-sectional study aimed to evaluate the association between preoperative PLR and positive sentinel lymph node biopsy (SLNB) in early breast cancer. Secondary objectives included assessing the relationship between positive SLNB and clinico-pathological features. Preoperative PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count, with a cut-off value of 127.1, determined by receiver operating characteristics (Area under the curve = 0.53). Statistical

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analysis was performed using the Pearson Chi-Square test. Among 271 women with early breast cancer who underwent SLNB, 17.7% (n = 48) had positive SLNB. No significant correlation was found between PLR and SLNB positivity (p = 0.193). However, high PLR was significantly associated with Chinese ethnicity (OR 2.524, 95% CI 1.05-6.069, p = 0.039). In conclusion, preoperative PLR does not predict SLNB positivity in early breast cancer and may not be suitable as an independent preoperative tool for assessing sentinel lymph node metastasis. Further research is required to explore alternative predictive markers.

Keywords: Breast cancer; lymphocyte; platelet; sentinel lymph node biopsy

INTRODUCTION

Breast cancer is a prevalent and critical global health issue, representing approximately 25% of all cancer cases worldwide (Zhang et al. 2017). In Malaysia; it stands as the leading malignancy among females and the primary cause of cancer-related mortality. The National Cancer Registry of Malaysia in 2004 reported a notable incidence rate of 46.2 per 100,000 women, translating to 1 in 20 women developing breast cancer in their lifetime (Subha 2019; Yip et al. 2006). Nodal metastasis is one of the well-established prognostic factors guiding treatment decisions (Yip et al. 2014)

Early breast cancer is characterised by a tumour measuring < 5cm, with histologically confirmed metastasis 1-3 axillary nodes (T2N1). For patients with clinically undetectable axillary nodes preoperatively, sentinel lymph node biopsy (SLNB) is the standard surgical procedure for intraoperative assessment of axillary nodal metastasis. In cases where histological examination reveals metastasis of more than 3 nodes, completion of axillary nodes level II dissection is performed to minimise risk of regional recurrence (Menon at al. 2024). Currently, no single biomarker has demonstrated sufficient reliability to predict axillary node metastasis pre-operatively, making the SLNB remains as the gold standard to provide balance between diagnostic accuracy and minimised procedural morbidity (Patani et al. 2007). Recent studies have emphasised the intricate relationship between inflammation and cancer progression, prompting exploration into blood parameters, including the platelet-to-lymphocyte ratio (PLR), as potential indicators of systemic inflammatory responses in cancer (Chen et al. 2020a)

While various prognotic factors for breast cancer have been extensively studied, the specific role of the PLR in predicting positive SLNB in early breast cancer remains unclear. Despite the established significance of inflammatory cells, including platelets and lymphocytes in the tumor microenvironment, the precise association between pre-operative PLR and SLNB positivity is yet to be fully elucidated. The existing literature has shown conflicting results regarding the predictive value of PLR, necessitating further investigation to determine its reliability as a predictive biomarker for lymph node involvement in early breast cancer (Bahgat 2017; Kim et al. 2019; Krenn-Pilko et al. 2014; Takada et al. 2020; Sejati et al. 2019)

This study was undertaken to address the current knowledge regarding the association between PLR and SLNB in early breast cancer. Despite the extensive research on predictive factors, the role of PLR, which reflects the balance between platelet-promoted tumour progression and lymphocyte-mediated immune surveillance, requires comprehensive exploration. By conducting a single-center, cross-sectional study in a tertiary hospital, we aimed to determine the relationship between preoperative PLR and SLNB positivity. Additionally, the investigation sought to examine associations between clinico-pathological features and positive SLNB, providing insights into factors influencing lymph node metastasis in early breast cancer.

MATERIALS AND METHODS

Patients

The is a cross sectional study encompassed the retrospective collection of clinicopathologic data from patients treated at Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, spanning from January 2009 to December 2022. The sampling method was consecutive sampling with strict inclusion and exclusion criteria ensuring the selection of subjects relevant to study objectives. Inclusion criteria comprised of female patients diagnosed with clinically early invasive breast cancer and devoid of distant metastasis at the time of diagnosis. Included patients underwent either mastectomy or breast-conserving surgery, coupled with SLNB. Additionally, the subjects had platelet and lymphocyte counts within one week preceding surgery and complete clinicopathologic information, including detailed histopathological examinations. Exclusion criteria involved patients with multiple malignancies, connective tissue disease, hematological disorders, retroviral diseases, as well as those on antimetabolites or immunosuppressant drugs.

This study drew upon findings from a multicenter retrospective analysis on SLNB in early breast cancer in China, which reported a 17.5% incidence of positive sentinel lymph nodes (Zhang et al. 2020). The sample size for this cross-sectional study was determined using the prevalence formula proposed by Danial 1999 (Pourhoseingholi et al. 2013). Setting prevalence (P) at 0.17, confidence level (Z) at 1.96, and precision (d) at 0.05 resulted in a calculated sample size (n) of 222 patients. Factoring in an estimated dropout rate of 20%, the final required sample size was determined to be 266 subjects.

$$n = Z^2 \frac{P(1-P)}{d^2}$$

$$n = 1.96^2 \times \frac{0.17(1-0.17)}{0.05^2}$$

$$n = 222 \text{ subjects}$$

Adding on dropout rate 20%, sample size ~ 266 subjects

Classification Criteria for Patients

This study employed a classification system for breast cancer subtypes (BCS) that included HR+/HER2- (ER+, PR+, HER2-), HR+/HER2+ (ER+, PR+, HER2+), HR-/HER2+ (ER-, PR-, HER2+) and HR-/HER2- (ER-, PR-, HER2-). Hormone receptor (HR) positivity was defined as the presence of more than 1% of ER and PR positive cells, as determined by immunohistochemistry. Meanwhile, HER2 positivity was identified by grade 2+ and 3+, assessed through gene amplification using dual in situ hybridisation (DISH).

Adhering to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system, tumor size is categorised based on its greatest dimension, with T1 (≤ 20 mm), T2 (> 20 mm - ≤ 50 mm), and T3 (> 50 mm) classifications. The presence of tumor cells in the axillary sentinel lymph node was defined as sentinel lymph node metastasis, encompassing both macrometastasis (> 2 mm) and micrometastasis (≤ 2 mm).

Statistical Analysis

The PLR for the study participants was computed by dividing the absolute count of platelets by the absolute count of lymphocytes.

$$PLR = \frac{\text{Absolute platelet count}}{\text{Absolute lymphocyte count}}$$

In order to establish the predictive cut-off value for this ratio, receiver operating characteristics (ROC) curve analysis was conducted. Subsequent data analysis was performed using the Statistical Packages for the Social Sciences (SPSS) for Windows version 27 (IBM Corp, Armonk, New York). Pearson's Chi-square test was employed to assess the association between the PLR ratio and positive SLNB, along with various clinicopathologic features. Statistical significance was acknowledged when the p-value < 0.05. This systematic approach ensured a comprehensive examination of the relationship between PLR and the outcomes of interest in the context of early breast cancer.

Ethics Approval

This study was approved by the Research Ethics Committee, Universiti Kebangsaan Malaysia (JEP-2021-362). This was a retrospective study based on the review of existing medical records; therefore the requirement for written consent was waived by the ethics committee. All data were handled confidentially and anonymised prior to analysis.

RESULTS

ROC Curve for PLR

ROC curve analysis for the PLR demonstrated an area under the curve (AUC) of 0.53 as depicted in Figure 1. The optimal cut off value for distinguishing between high and low PLR determined through analysis of the mean distribution is 127.1. At this threshold, the sensitivity was 52.5% and specificity was 57.5%. Meanwhile, the positive predictive value was 31% and negative predictive value was 76.69%.

Sociodemographic Characteristics

This study reviewed the medical records of 271 women diagnosed with clinically early breast cancer and underwent SLNB. The mean age of the patients at the time of detection was 55.8 ± 11.6 years. Regarding racial distribution, the study included 162 (59.8%) Malay, 81 (29.9%) Chinese, 17 (6.3%) Indian and 11 (4.2%) individuals from other ethnicities. Table 1 summarised the sociodemographic characteristics of the study population.

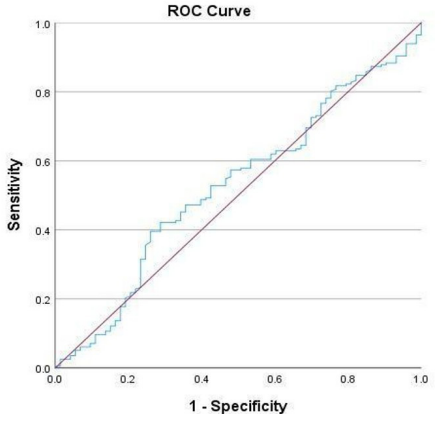

FIGURE 1: Receiver operating characteristics (ROC) curve for platelet-to-lymphocyte ratio (PLR)

Distribution of Platelet-Lymphocyte Count and Ratio

Table 2 presented a summary of the median and mean values for platelets and lymphocytes. The median platelet count was 266 (IQR; 223 to 318), and the median lymphocyte count was 2 (IQR; 1.6 to 2.7). Furthermore, considering both cell counts, the median platelet-lymphocyte ratio was 127.1 (IQR; 101.0 to 159.5).

TABLE 1: Sociodemographic characteristics

Parameters	Number of patients (n = 271), n (%)
Age	
Younger than 60	165 (60.9%)
Older than 60	106 (39.1%)
Ethnicity	
Malay	162 (59.8%)
Chinese	81 (29.9%)
Indian	17 (6.3%)
Others	11 (4.2%)

n: Number of patients

TABLE 2: Mean and median for platelet-lymphocyte count and ratio

Parameters	Value, Median (IQR)
Platelet count	266 (IQR; 223 to 318)
Lymphocyte count	2 (IQR; 1.6 to 2.7)
Platelet-lymphocyte ratio	127.1 (IQR; 101.0 to 159.5)

IQR: Interquartile range

Clinicopathological Characteristics

Table 3 provided a comprehensive description of the clinicopathological characteristics observed in the patients included in this study. The distribution of affected breast sides was found to be comparable. Wide local excision emerged as the most frequently performed surgical procedure, with Invasive carcinoma of no specific type (NST) constituting the majority of histological diagnoses, accounting for 230 patients (84.9%). Tumour size analysis revealed that T1 and T2 tumours occurred in almost equal numbers, while Grade II tumours accounted for half of the overall grade, with 141 patients. The lymphovascular invasion (LVI) positivity rate was determined to be 26.2% (n = 71). Among the luminal subtypes, HR+/HER2- was the most prevalent, comprising 64.6% (n = 175) of cases. This study identified a sentinel lymph node metastasis rate of 17.7% (n = 48).

TABLE 3: Clinico-pathological features

Parameters	Number of patients (n = 271), n (%)
Side	
Right	135 (49.8%)
Left	136 (50.2%)
Types of Surgery	
WLE	169 (62.4%)
Mastectomy	77 (28.4%)
HWL + WLE	24 (8.9%)
Microdochectomy	1 (0.3%)
Histopathology	
Invasive Carcinoma (NST)	230 (84.9%)
Invasive Lobular	13 (4.8%)
Invasive Papillary	10 (3.7%)
Invasive Mucinous	11 (4.1%)
Invasive Apochrine	1 (0.4%)
Medullary Carcinoma	3 (1.1%)
Metaplastic Carcinoma	2 (0.7%)
Adenoid Cystic Carcinoma	1 (0.4%)
Tumour Size	
T1	127 (46.9%)
T2	138 (50.9%)
T3	6 (2.2%)
Tumour Grade	
I	78 (28.8%)
II	141 (52.0%)
III	52 (19.2%)
LVI	
Positive	71 (26.2%)
Negative	200 (73.8%)
BCS	
HR+/HER2-	175 (64.6%)
HR+/HER2+	27 (10.0%)
HR-/HER2+	28 (10.3%)
HR-/HER2-	41 (15.1%)
SLNB outcome	
Positive	48 (17.7%)
Negative	223 (82.3%)

n: number of patients; WLE: Wide local excision; HWL: Hook wire localisation; NST: No specific type; LVI: Lymphovascular invasion; BCS: Breast Cancer Subtypes; HR: Hormone receptor; HER2: Human epidermal growth factor 2; SLNB: Sentinel lymph node biopsy

Association of High PLR with SLNB outcome

Table 4 illustrated the relation between elevated PLR and SLNB outcome. The analysis revealed no significant association between high PLR and SLB metastasis, as indicated in Table 4.

Association of High PLR with Ethnicity

Univariate analysis demonstrated a significant association between elevated PLR and Malay and Chinese ethnicities. Multivariate analysis, detailed in Table 5, further identified Chinese ethnicity as independently associated with high PLR values (OR 2.524, 95% CI 1.05-6.069, $p < 0.039$).

Association between High PLR and Clinicopathological Features

Table 6 delineated the relationship between elevated PLR and clinicopathological features of breast cancer. The analysis indicated no notable association between high PLR levels and the examined clinico-pathological features, as

TABLE 4: Association between high PLR Ratio and SLNB outcome

Parameters	SLNB Positive, n (%)	SLNB Negative, n (%)	Chi Square value	p-value
High PLR Ratio (Cut off value 127.1)	28 (20.7%)	107 (79.3%)	5.089	0.193
Low PLR Ratio	17 (6.3%)	119 (43.9%)	2.75	0.097

*Chi-square analysis was used in this analysis
PLR: Platelet-lymphocyte ratio; SLNB: Sentinel lymph node biopsy

TABLE 5: Association between high PLR and ethnicity

Parameters Ethnicity	Univariate Analysis			Parameters Ethnicity	Multivariate Analysis		
	Odds ratio	95% CI	p-value		Odds ratio	95% CI	p-value
Malay	0.350	0.193, 0.636	< 0.001	Malay	1.014	0.451, 2.282	0.972
Chinese	3.403	1.861, 6.223	< 0.001	Chinese	2.524	1.050, 6.069	0.039
Indian	0.471	0.105, 2.123	0.327				
Others	1.398	0.359, 5.445	0.629				

*Binary logistic regression analysis was used in this analysis; *Reference group for ethnicity is Malay
PLR: Platelet-lymphocyte ratio

TABLE 6: Association between high PLR and clinic-pathological features

Parameters	Univariate Analysis		
	Odds ratio	95% CI	p-value
Histopathology			
Invasive carcinoma (NST)	1.050	0.54, 2.041	0.886
Invasive lobular	0.615	0.196, 1.931	0.405
Invasive medullary	0.500	0.045, 5.580	0.573
Invasive papillary	2.424	0.614, 9.580	0.207
Invasive mucinous	0.833	0.248, 2.799	0.768
Invasive apocrine	-	-	-
Metaplastic carcinoma	-	-	-
Adenoid cystic carcinoma	-	-	-
Tumour Size			
T1	0.689	0.427, 1.113	0.128
T2	1.462	0.901, 2.373	0.124
T3	1.228	0.239, 6/319	0.806
LVI			
Positive	1.049	0.611, 1.804	0.862
Negative	0.953	0.554, 1.638	0.862

Continue...

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Parameters	Univariate Analysis		
	Odds ratio	95% CI	p-value
BCS			
HR+/HER2-	0.989	0.601, 1.627	0.964
HR+/HER2+	1.095	0.494, 2.435	0.824
HR-/HER2+	1.938	0.860, 4.370	0.111
HR-/HER2-	0.597	0.303, 1.177	0.136

*Binary logistic regression analysis was used in this analysis.
WLE: Wide local excision; HWL: Hook wire localisation; NST: No specific type; LVI: Lymphovascular invasion; BCS: Breast cancer subtypes; HR: Hormone receptor; HER2: Human epidermal growth factor 2; SLNB: Sentinel lymph node biopsy

depicted in the table.

Association between Positive SLNB in Early Breast Cancer with Clinicopathological Features

Table 7 presented a comprehensive summary of the univariate analysis conducted to investigate the correlation between positive SLNB and clinicopathological features. The findings revealed positive SLNB was significantly associated with tumour size classified with T1 (OR 0.238, 95%CI 0.11-0.50, $p < 0.001$) and T2 (OR 3.559, 95%CI 1.76-7.2, $p < 0.001$). In addition, tumour grade was significantly associated with SLNB positivity, with grade 1 (OR 0.3, 95%CI 0.122-0.74), $p = 0.009$) and grade III tumour (OR 2.597, 95%CI 1.29-5.22), $p = 0.007$). However, multivariate analysis was summarised in Table 8, did not demonstrate a statistically significant association between positive SLNB and tumour size or grade.

DISCUSSION

Our study aimed to explore the association between preoperative PLR and positive SLNB in early breast cancer. The primary finding revealed an incidence rate of 17.7% for positive SLNB in our cohort, which closely aligns with global incidences reported in the literature. For instance, Takada et al. (2020) reported an incidence of 18.3%, while Minami et al. (2021) reported an incidence of 17.3%, further supporting our findings. Notably, this study represents the first investigation within the Malaysian context regarding the incidence rate of positive SLNB in early breast cancer.

Due to the potential risks and morbidities associated with axillary node dissection in breast cancer patients, SLNB has become a widely recognised approach for identifying sentinel axillary lymph node metastasis, particularly in early-stage breast cancer. In order to enhance the sensitivity of detection, extensive research has been conducted to explore the association between biochemical markers and SLNB positivity. Recognising the role of inflammatory cells in cancer progression and tumor surveillance, an increasing number of studies have investigated the potential of the PLR as a predictor of sentinel lymph node metastasis risk. To date, there is a gradual rise in figures of data available on the association between a high PLR ratio and poor outcomes or lymph node metastasis in various cancers, including breast cancer.

Despite the rising interest in utilising PLR as a predictive biomarker for lymph node involvement, our results did not demonstrate a significant correlation between high PLR and positive SLNB. This finding contrasts with some existing literature, such as the study by Takada et al. (2020) and Zhang et al. (2017), which observed a significant association of positive SLNB in the high preoperative PLR group. Our results emphasise the need for context-specific research and caution against universal assumptions

TABLE 7: Univariate analysis of association between positive SLNB in early breast cancer with clinico-pathological features

Parameters	Univariate Analysis		
	Odds ratio	95% CI	p-value
Histopathology			
Invasive carcinoma (NST)	0.604	(0.224, 1.629)	0.319
Invasive lobular	1.193	(0.256, 5.567)	0.822
Invasive medullary	-	-	-
Invasive papillary	0.856	(0.176, 4.163)	0.847
Invasive mucinous	2.207	(0.276, 17.658)	0.456
Invasive apocrine	-	-	-
Metaplastic carcinoma	-	-	-
Adenoid cystic carcinoma	-	-	-
Tumour Size			
T1	0.24	(0.113, 0.502)	< 0.001
T2	3.56	(1.759, 7.198)	< 0.001
T3	2.38	(0.423, 13.385)	0.325
Tumour Grade			
I	0.3	(0.122, 0.737)	0.009
II	1.11	(0.594, 2.075)	0.744
III	2.597	(1.292 – 5.220)	0.007
LVI			
Positive	1.925	(0.994, 3.726)	0.052
Negative	0.520	(0.268, 1.006)	0.052
BCS			
HR+/HER2-	0.897	(0.470, 1.710)	0.740
HR+/HER2+	1.374	(0.523, 3.611)	0.519
HR-/HER2+	1.305	(0.499, 3.416)	0.587
HR-/HER2-	0.767	(0.303, 1.942)	0.576

*Binary logistic regression analysis was used in this analysis.
n: number of patients; WLE: Wide local excision; HWL: Hook wire localisation; NST: No specific type; LVI: Lymphovascular invasion; BCS: Breast cancer subtypes; HR: Hormone receptor; HER2: Human epidermal growth factor 2; SLNB: Sentinel lymph node biopsy
*Reference groups were as follows: Histopathology-invasive carcinoma (NST), Tumour size-T1, Tumour Grade-Grade1, LVI-Negative, BCS-HR+/Her2-

TABLE 8: Multivariate analysis of association between positive SLNB in early breast cancer with tumour size and grade

Parameters	Multivariate Analysis		
	Odds ratio	95% CI	p-value
Tumour Size			
T1	2.043	(0.337, 12.381)	0.437
T2	2.147	(0.364, 12.668)	0.399
Tumour Grade			
I	1.166	(0.529, 2.571)	0.703
III	0.526	(0.242, 1.143)	0.105

*Binary logistic regression analysis was used in this analysis

regarding the predictive value of PLR across diverse populations. Chinese patients showed a significant association with high PLR in our cohort. In line with Malaysian data presented by Koh et al. (2015), the Chinese population had a higher likelihood of having elevated PLR compared to other ethnic groups. Hence, ethnicity could be a confounder which requires further study. The lack of a significant correlation between PLR and positive SLNB in our study may be attributed to the diverse ethnic composition of our cohort. Furthermore, the absence of similar association in our local study may be explained by several factors. Takada et al. (2020) and Zhang et al. (2017) predominantly examined Japanese and Chinese populations respectively. Variation in genetic predispositions, inflammatory responses and immune modulation across different ethnicities could influence PLR baseline value. Koh et al. (2015) highlighted that haematological markers, including PLR, vary significantly among ethnic groups due to genetic and environmental factors. Additionally, differences in sample size and statistical power between studies may contribute to the contrasting findings. A smaller sample size in the local study could reduce its sensitivity to detect subtle associations that might be apparent in larger or more homogenous cohorts.

Our investigation also highlights the relationship of clinicopathological features in predicting SLNB status. Traditionally, tumour size and histological grading have been recognised as independent risk factors for sentinel lymph node metastasis. Ding et al. (2017) conducted a study analysing 561 breast cancer patients who underwent breast surgery and SLNB. Their logistic regression analysis revealed a significant association between tumour size and grade with positive SLNB. In fact, Chen et al. (2020b) developed a recent risk prediction model in China, incorporating tumor size more than 2 cm and invasive ductal carcinoma type to evaluate the higher likelihood of sentinel lymph node metastasis in breast cancer patients. Despite these findings, our study did not demonstrate any statistically significant association between clinicopathological features and positive SLNB. Further robust studies with larger sample sizes and multicenter approaches are warranted to validate these parameters for assessing the likelihood of sentinel lymph node metastasis in early breast cancer patients.

Several limitations need consideration. The study was conducted at a single center with a relatively small sample size, potentially limiting the generalisability of our results. The determination of the PLR cutoff value through ROC analysis resulted in a low AUC value, reflecting the complexity of establishing a universally accepted threshold for PLR. The thresholds for high PLR classification may differ across studies.

CONCLUSION

In our study, we did not observe a significant association between a high PLR and positive SLNB in early breast cancer. However, we found that elevated PLR has a relationship with Chinese ethnicity. This information holds immense importance as it provides crucial evidence for the researchers to engage in a more detailed study of the potential role of PLR in predicting SLNB outcomes in early breast cancer within the multiethnicity population.

Author contributions: Study design, data collection, manuscript-original draft: SES; Statistical analysis: SAH; Data interpretation: SES, SAH; Clinical guidance: AS; Supervision: SNAS; AS; Manuscript-review and editing: SNAS, AS, SAS. All authors have approved the final manuscript.

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Ethical statement: Ethical approval was obtained from the Research Ethics Committee, Universiti Kebangsaan Malaysia (JEP-2021-362). This study was performed in accordance with institutional ethical standards. Patient data were collected retrospectively and handled with confidentiality

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