

**Keywords:** breast cancer; survival; neutrophil lymphocyte ratio; platelet lymphocyte ratio; Asia

# Utility of pre-treatment neutrophil–lymphocyte ratio and platelet–lymphocyte ratio as prognostic factors in breast cancer

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**Background:** Peripheral blood-derived inflammation-based scores such as the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) have recently been proposed as prognostic markers in solid tumours. Although evidence to support these markers as unfavourable prognostic factors is more compelling in gastrointestinal cancers, very little is known of their impact on breast cancer. We investigated the association between the NLR and PLR, and overall survival after breast cancer.

**Methods:** Data from the University of Malaya Medical Centre Breast Cancer Registry was used. Of 2059 consecutive patients diagnosed from 2000 to 2008, we included 1435 patients with an available pre-treatment differential blood count (~70%). Patients were stratified into quintiles of the NLR/PLR. Multivariable Cox regression was used to determine the independent prognostic significances of the NLR/PLR.

**Results:** Compared with the first quintile of the NLR, women in quintile 5 were younger, had bigger tumours, nodal involvement, distant metastases and higher tumour grades. Higher NLR quintiles were significantly associated with poorer survival with a 5-year relative survival ratio (RSR) of 76.4% (95% CI: 69.6–82.1%) in quintile 1, 79.4% (95% CI: 74.4–83.7%) in quintile 2, 72.1% (95% CI: 66.3–77.3%) in quintile 3, 65.6% (95% CI: 59.8–70.8%) in quintile 4 and 51.1% (95% CI: 43.3–58.5%) in quintile 5. Following adjustment for demography, tumour characteristics, treatment and the PLR, the adjusted hazard ratio (HR) for quintile 5 vs quintile 1 was 1.50 (95% CI: 1.08–1.63);  $P_{\text{trend}} = 0.004$ . Results were unchanged when the NLR was analysed as a dichotomous variable using different cutoff points. Although patients in PLR quintile 5 had lower survival than in quintile 1 (5-year RSR: 53.2% (95% CI: 46.9–59.2%) vs 77.0% (95% CI: 70.9–82.2%)), this association was not significant after multivariable adjustment. However, a PLR > 185 was significantly associated with poorer survival; adjusted HR: 1.25 (95% CI: 1.04–1.52).

**Conclusions:** Both the NLR and PLR are independently associated with an increased risk of mortality in breast cancer. Their added value in the prognostication of breast cancer in clinical practice warrants investigation.

Cancer progression and prognosis are affected by the host's inflammatory response in the tumour microenvironment (Hanahan and Weinberg, 2011). As components of systemic inflammatory response, lymphocytes, neutrophils, and platelets are increasingly being recognised to have an important role in

carcinogenesis and tumour progression (DeNardo and Coussens, 2007; Gregory and Houghton, 2011; Lal *et al*, 2013). To date, a number of peripheral blood-derived inflammation-based scores such as the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and Glasgow Prognostic Score have been

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proposed as prognostic markers in cancer (Roxburgh and McMillan, 2010; Proctor *et al*, 2011; Guthrie *et al*, 2013).

Evidence to support NLR as an unfavourable prognostic factor is most compelling in colorectal cancer (Li *et al*, 2014). Likewise, an elevated PLR has been found to adversely impact survival in gastrointestinal cancers (Templeton *et al*, 2014a). However, the role of these biomarkers in breast cancer prognosis is less well known (Azab *et al*, 2012, 2013; Noh *et al*, 2013; Dirican *et al*, 2014; Krenn-Pilko *et al*, 2014; Nakano *et al*, 2014). To date, several studies have shown that an increased NLR is associated with lower survival (Azab *et al*, 2012, 2013; Noh *et al*, 2013; Dirican *et al*, 2014; Nakano *et al*, 2014), whereas one study has shown that the PLR may also be an adverse prognostic marker in breast cancer (Krenn-Pilko *et al*, 2014).

The NLR and PLR can be derived from the full blood count, and may therefore provide a simpler and cheaper avenue for breast cancer prognostication. Validating the findings of previous studies within a large prospective cohort of breast cancer patients in a different setting will hence be useful in elucidating the prognostic role of the NLR and PLR in women with breast cancer. We investigated the association between the pre-treatment NLR and PLR and survival following breast cancer in a large Asian cohort.

## PATIENTS AND METHODS

Data for this study were obtained from the Breast Cancer Registry of the University of Malaya Medical Centre (UMMC), Malaysia. Prospective registration of newly diagnosed breast cancer patients began at the UMMC in 1993. The Registry, which obtained ethical approval from the Institutional Review Board, currently retains detailed data on patients' demographic, tumour and treatment characteristics (Pathy *et al*, 2011).

In the year 2000, a fully computerised online laboratory system was introduced at the UMMC, which allows for the tracing of patients' blood count results. Hence, we included women diagnosed from the year 2000 onwards. Only pre-operative blood count results (counts taken as part of pre-operative assessment) or counts taken before systemic therapy/radiotherapy in those who did not undergo surgery were considered in this study. Of the 2059 consecutive patients diagnosed between 1 January 2000 and 31 December 2008, we have included 1435 patients with available data for pre-treatment differential blood counts (~70%).

**Study variables.** In order to ascertain that the blood count results that were extracted from the hospital's online records were pre-treatment values, we crosschecked the dates of the initial treatment initiation for each patient, against the date when the complete blood count was performed. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

The data on the patient's demography included age at diagnosis, and self-reported ethnicity (Malay, Chinese, Indian, or other race). The variables for the tumour characteristics included pathologically determined tumour size (cm), the number of histologically positive lymph nodes, oestrogen receptor (ER)/progesterone receptor (PR) status (positive when >10% of tumour cells stained positive during immunohistochemical (IHC) testing, negative otherwise), tumour grade (Scarff—Bloom—Richardson classification; grade 1, grade 2, grade 3), lymphovascular invasion (LVI) (present, absent), and HER2 status (positive when IHC testing = 3+, negative when IHC testing = 0 or 1+). Tumours with equivocal HER2 status (2+) were subjected to fluorescence *in situ* hybridisation to confirm HER2 positivity. All patients diagnosed prior to January 2003 were restaged using AJCC6 criteria. In 164

patients whom did not undergo surgery, clinically determined tumour size, and axillary lymph node status were used.

Loco-regional treatment data included surgery (no surgery, mastectomy, breast-conserving surgery, adjuvant radiotherapy (yes, no), and surgical margin status (positive, negative)). Systemic treatment data comprised of neoadjuvant chemotherapy (yes, no), adjuvant chemotherapy (no chemotherapy, yes: first generation, yes: second generation (anthracycline based), yes: third generation (taxane based)), and endocrine therapy (yes, no).

**Follow-up and outcome assessment.** Patients were followed-up in the breast clinic. Vital status was determined through direct linkage with the Malaysian National Registration Department. The follow-up time was calculated from the date of diagnosis to the date of death, or was censored at the end of follow-up (1 February 2014). The cause of death and the data on disease recurrence were only sparsely available.

**Statistical analysis.** Categorical variables were compared using the  $\chi^2$ -test. Continuous variables were expressed in medians and were compared using the Kruskal–Wallis test. Patients were stratified into the quintiles of the NLR/PLR (quintile 1, quintile 2, quintile 3, quintile 4, quintile 5). The demographic, tumour, and treatment characteristics were compared between the quintiles. Multivariable logistic regression was performed to identify factors that were independently associated with an elevated NLR/PLR. For this purpose, elevations of the NLR and PLR were defined using cutoff values of 4.0 (Dirican *et al*, 2014; Templeton *et al*, 2014b) and 185 (Azab *et al*, 2013; Templeton *et al*, 2014a), respectively.

To approximate disease-specific survival, we computed relative survival, which is a widely employed measure of cancer survival, given that it does not rely on an accurate cause of death coding (Dickman *et al*, 2004; Coleman *et al*, 2008). The relative survival ratio (RSR) is the ratio of overall (all-cause) survival observed in breast cancer patients to the survival that would have been expected had they been subjected only to the background mortality rates of the general female population (matched for age, and calendar year). Expected survival was derived from the Malaysian life tables. The RSR between the five quintiles of the NLR/PLR were compared.

We used multivariable Cox regression analysis to estimate the relative risk of all-cause mortality in each quintile of the NLR/PLR with quintile 1 as the reference, adjusted for all of the previously mentioned variables. Given that both the NLR and PLR are positively associated with increased risk of cancer mortality (Templeton *et al*, 2014a,b), we mutually adjusted the NLR and PLR against each other.

Previous studies, which investigated the prognostic role of the NLR/PLR have used different cutoff points to define the NLR/PLR elevation. We performed sensitivity analyses using these different cutoff values; NLR: 3.00 (Templeton *et al*, 2014b), 4.00 (Dirican *et al*, 2014; Templeton *et al*, 2014b) and PLR: 185 (Azab *et al*, 2013), 292 (Krenn-Pilko *et al*, 2014).

As some studies have shown that the NLR and PLR may only be of prognostic value in certain breast cancer subtypes, we assessed for effect modification (Noh *et al*, 2013; Krenn-Pilko *et al*, 2014). Patients were classified as having one of four subtypes of breast cancer; ER-positive or PR-positive and HER2-negative tumours (ER+/PR+ and HER-), ER-positive or PR-positive and HER2-positive tumours (ER+/PR+ and HER2+), ER-negative and PR-negative and HER2-positive tumours (ER- and PR- and HER2+), and ER-negative and PR-negative and HER2-negative tumours (ER- and PR- and HER2-). We performed a log likelihood ratio test by including an interaction term 'breast cancer subtype (four groups) multiplied by the NLR/PLR (in two categories using cutoff values of 4.0 and 185, respectively)' into the main Cox model. As most of the subgroups were small, only the prognostic factors that changed the hazard ratio (HR) for an

elevated NLR/PLR by  $>10\%$  in the bivariable analyses were included in the multivariable model.

Missing values (ranging between 5 and 30%) were imputed by multiple imputation. All of the variables in the multivariable Cox regression were included in the imputation model and 10 imputation sets were created.

This study was approved and received ethical clearance from the Medical Ethics Committee of the UMMC (Inst/IRB/1024.73).

## RESULTS

The median age at diagnosis was 52 years. A majority of patients were Chinese (58%), followed by Malays (25%), Indians (16%), and other races (1%). The median tumour size at diagnosis was 3.5 cm. Approximately half of the patients had lymph node involvement. At initial diagnosis, about 22% of women presented with (AJCC6) stage I, followed by 34% with stage II, 30% with stage III, and 14% with stage IV breast cancer.

The median pre-treatment NLR and PLR were 2.2 and 144, respectively. The cutoff values for the categorisation of the NLR into quintiles were 1.39, 2.00, 2.58, and 4.00. Patients in the lower NLR quintile (quintiles 1 and 2) were significantly older than those in the higher quintiles (Table 1). Chinese patients were more likely to have a high NLR compared with Indians. Tumour size was positively associated with the NLR. Higher NLR quintiles were more likely to be associated with lymph node involvement than the lower two quintiles. The proportion of patients with *de novo* metastatic breast cancer was remarkably higher in NLR quintile 5. Higher NLR quintiles were also significantly associated with unfavourable tumour characteristics including higher tumour grade, LVI, lack of PR expression, and HER2 expression. Importantly, the NLR and PLR were positively correlated; Pearson coefficient regression = 0.586,  $P < 0.001$ . In a multivariable logistic regression, only HER2 expression, increasing tumour size, and PLR were significantly associated with an elevated NLR. Patients in NLR quintile 5 were least likely to have undergone any surgery. In women subjected to surgery, those in NLR quintile 5 were most likely to have received neoadjuvant chemotherapy (Table 1).

The cutoff values for the categorisation of PLR into quintiles were 100, 129, 161, and 215. A higher PLR was significantly associated with a younger age at diagnosis (Table 2). Chinese patients were more likely to have a higher PLR than the Indians. Tumour size and lymph node involvement were positively associated with the PLR. Patients in PLR quintile 5 were significantly associated with higher stages, particularly stage IV disease. Their tumours were also more likely to be associated with poor prognostic features such as LVI and HER2 expression. Following multivariable logistic regression, Chinese ethnicity, high nodal burden ( $>9$  nodes), distant metastasis, and an increasing NLR were associated with an elevated PLR. Patients in the higher PLR quintile were least likely to have undergone any surgery. A high neoadjuvant chemotherapy administration rate was also observed among patients in the higher PLR quintile who were candidates for surgery.

The RSR was highest in breast cancer patients in the lowest NLR quintile, whereas it was lowest in the highest NLR quintile (Figure 1). The 5-year RSRs were 76.4% (95% CI: 69.6–82.1%) in quintile 1, 79.4% (95% CI: 74.4–83.7%) in quintile 2, 72.1% (95% CI: 66.3–77.3%) in quintile 3, 65.6% (95% CI: 59.8–70.8%) in quintile 4, and 51.1% (95% CI: 43.3–58.5%) in quintile 5. The risk of death in patients in the highest NLR quintile was 2.5 times higher than for their counterparts in the lowest quintile (Table 3). In the multivariable analysis, both the NLR and PLR were found to be independently associated with survival. Patients in the highest NLR quintile remained significantly associated with a higher risk of

mortality than those in the lowest quintile following adjustment for demography, tumour characteristics, treatment, and PLR; HR: 1.50 (95% CI: 1.08–1.63);  $P$  for the linear trend test = 0.004.

Women with breast cancer in the highest quintile of the PLR were also found to have substantially lower survival rates than their counterparts in the other quintiles. The 5-year RSRs were 77.0% (95% CI: 70.9–82.2%) in quintile 1, 75.3% (95% CI: 69.4–80.5%) in quintile 2, 76.3% (95% CI: 70.4–81.4%) in quintile 3, 70.0% (95% CI: 64.0–75.4%) in quintile 4, and 53.2% (95% CI: 46.9–59.2%) in quintile 5 (Figure 2). Following multivariable adjustment for demographics, tumour characteristics, treatment, and the NLR, an increased PLR was no longer associated with an increased risk of death; the HR for quintile 5 was 1.07 (95% CI: 0.81–1.41) compared with quintile 1 (Table 3).

Sensitivity analyses using different cutoff levels for the NLR did not change the main results (Table 4). However, in a fully adjusted multivariable analysis, patients with a PLR  $>185$  were significantly associated with a higher risk of death compared with their counterparts with a PLR  $\leq 185$ . Using a cutoff of 292, a high PLR was not significantly associated with a risk of mortality following breast cancer (Table 4).

The breast cancer subtype did not appear to modify the association between the NLR/PLR and survival;  $P$ -values for interaction were 0.147 and 0.680, respectively. Subgroup analysis by subtype of breast cancer showed that an elevated NLR was significantly associated with an increased mortality in women with ER- and PR- breast cancer, irrespective of HER2 status (Table 5). On the contrary, an elevated PLR was independently associated with an increased risk of mortality in patients with ER+ or PR+ and HER2+ breast cancer (Table 5).

## DISCUSSION

In this study, a higher pre-treatment NLR was significantly and independently associated with higher mortality in women with breast cancer, with evidence of a dose-response relationship. The results remained robust despite using different cutoff values. Elevation of the pre-treatment PLR was also independently associated with breast cancer mortality. However, there was no evidence of a dose-response relationship, and the results could not be replicated when different cutoff levels were used.

An elevated NLR is associated with adverse survival probabilities in gastrointestinal cancers; namely, colorectal, stomach, liver, oesophageal, and pancreatic cancers (Walsh *et al*, 2005; Shimada *et al*, 2010; Sharaiha *et al*, 2011; Chiang *et al*, 2012; Limaye *et al*, 2013; Stotz *et al*, 2013; Xu *et al*, 2014). A very recent meta-analysis of 40 559 patients with solid tumours found that an NLR greater than 4.00 was associated with a substantial increase in risk for all-cause mortality (HR: 1.81, 95% CI: 1.67–1.97) (Templeton *et al*, 2014b). Although evidence on the prognostic role of the NLR in breast cancer has been relatively scarce (Azab *et al*, 2012, 2013; Noh *et al*, 2013; Dirican *et al*, 2014; Nakano *et al*, 2014; Yao *et al*, 2014), our robust results add valuable evidence that the NLR is also an adverse prognostic indicator in breast cancer. An earlier study in breast cancer patients, which stratified the NLR according to quartiles, reported that mortality was higher in the highest NLR quartile but closely similar among the lower three quartiles, suggesting a threshold effect (Azab *et al*, 2012). In our study, although the risk of mortality increased substantially with each NLR quintile in univariable analysis, the observation that this trend was attenuated after multivariable adjustment seems to suggest that the association between the NLR and mortality in breast cancer may not be entirely linear.

It has been suggested that optimal cutoff values for prognostic markers may be better selected by validating previously established

**Table 1. Demographic, tumour and treatment characteristics of 1435 women with breast cancer by quintiles of pre-treatment neutrophil-lymphocyte ratio**

	Overall	Quintile 1 NLR ≤ 1.39 n = 226	Quintile 2 1.39 < NLR ≤ 2.00 n = 379	Quintile 3 2.00 < NLR ≤ 2.58 n = 305	Quintile 4 2.58 < NLR ≤ 4.00 n = 331	Quintile 5 NLR > 4.00 n = 194	P <sup>a</sup>	Multivariable odds ratio <sup>b</sup> (96% CI)
Age (years), median	52	56	53	50	49	50	<0.001 <sup>c</sup>	1.00 (0.98–1.02)
<b>Race, n (%)</b>							0.011 <sup>c</sup>	
Chinese	830 (57.8)	115 (50.9)	216 (57.0)	176 (57.7)	204 (61.6)	119 (61.3)		1.00
Malay	363 (25.3)	54 (23.9)	89 (23.5)	82 (26.9)	86 (26.0)	52 (26.8)		0.81 (0.52–1.28)
Indian	222 (15.5)	55 (24.3)	68 (17.9)	42 (13.8)	36 (10.9)	21 (10.8)		1.00 (0.56–1.79)
Others	20 (1.4)	2 (0.9)	6 (1.6)	5 (1.6)	5 (1.5)	2 (1.054)		0.80 (0.17–3.84)
Tumour size (cm) <sup>d</sup> , median	3.5	3.0	3.0	3.5	4.0	5.0	<0.001 <sup>c</sup>	1.06 (1.01–1.10) <sup>c</sup>
<b>No. of positive axillary lymph nodes, n (%)</b>								
0	639 (51.7)	115 (54.0)	190 (55.1)	150 (55.1)	126 (45.8)	58 (44.6)	0.142	1.00
1–3	285 (23.1)	49 (23.0)	69 (20.0)	65 (23.9)	64 (23.3)	38 (29.2)		1.21 (0.74–1.96)
4–9	170 (13.8)	29 (13.6)	44 (12.8)	27 (9.9)	49 (17.8)	21 (16.2)		1.14 (0.62–2.09)
≥ 10	141 (11.4)	20 (9.4)	42 (12.2)	30 (11.0)	36 (13.1)	13 (10.0)		0.47 (0.22–1.04)
Unknown	200							
<b>Distant metastasis, n (%)</b>							<0.001 <sup>c</sup>	
None	1222 (86.1)	210 (93.3)	348 (92.1)	265 (87.7)	272 (83.4)	127 (67.6)		1.00
Present	197 (13.9)	15 (6.7)	30 (7.9)	37 (12.3)	54 (16.6)	61 (32.4)		1.28 (0.72–2.27)
Unknown	16							
<b>Grade, n (%)</b>							0.019 <sup>c</sup>	
1	83 (7.7)	13 (7.3)	22 (7.5)	24 (10.1)	20 (8.2)	4 (3.3)		1.00
2	514 (48)	104 (58.4)	125 (42.7)	111 (46.8)	119 (49.0)	55 (45.8)		1.43 (0.44–4.69)
3	474 (44.3)	61 (34.3)	146 (49.8)	102 (43.0)	104 (42.8)	61 (50.8)		1.44 (0.45–4.63)
Unknown	364							
<b>Lymphovascular invasion, n (%)</b>							0.279	
None	552 (53.4)	96 (55.8)	167 (54.9)	125 (56.6)	111 (50.0)	53 (46.1)		1.00
Present	482 (46.6)	76 (44.2)	137 (45.1)	96 (43.4)	111 (50.0)	62 (53.9)		1.07 (0.65–1.77)
Unknown	401							
<b>Oestrogen receptor status, n (%)</b>								
Negative	612 (44.9)	105 (47.3)	156 (42.2)	122 (42.1)	137 (44.1)	92 (54.1)	0.075	1.00
Positive	751 (55.1)	117 (52.7)	214 (57.8)	168 (57.9)	174 (55.9)	78 (45.9)		0.83 (0.49–1.43)
Unknown	72							
<b>PR status, n (%)</b>							0.026 <sup>c</sup>	
Negative	617 (51.2)	107 (53.8)	161 (47.6)	123 (47.1)	141 (52.2%)	85 (62.5%)		1.00
Positive	587 (48.8)	92 (46.2)	177 (52.4)	138 (52.9)	129 (47.8%)	51 (37.5%)		0.81 (0.44–1.47)
Unknown	231							
<b>HER2 status, n (%)</b>							0.002 <sup>c</sup>	
Negative	699 (55.1)	122 (58.4)	204 (58.3)	171 (62.6)	137 (48.4)	65 (42.5)		1.00
Positive	456 (36.0)	71 (34.0)	119 (34.0)	80 (29.3)	116 (41.0)	70 (45.8)		1.52 (1.02–2.26) <sup>c</sup>
Equivocal	113 (8.9)	16 (7.7)	27 (7.7)	22 (8.1)	30 (10.6)	18 (11.8)		1.67 (0.85–3.27)
Unknown	167							
PLR, median	144	96	119	147	185	263	0.000 <sup>c</sup>	1.01 (1.01–1.02) <sup>c</sup>
<b>Surgery, n (%)</b>							0.000 <sup>c</sup>	—
None	164 (11.4)	11 (4.9)	24 (6.3)	25 (8.2)	47 (14.2)	57 (29.4)		
Mastectomy	989 (68.9)	163 (72.1)	272 (71.8)	209 (68.5)	228 (68.9)	117 (60.3)		
BCS	282 (19.7)	52 (23.0)	83 (21.9)	71 (23.3)	56 (16.9)	20 (10.3)		
<b>Radiotherapy, n (%)</b>							0.546	—
Yes	835 (62.3)	138 (64.8)	219 (60.8)	189 (63.9)	192 (63.4)	97 (57.4)		
None	506 (37.7)	75 (35.2)	141 (39.2)	107 (36.1)	111 (36.6)	72 (42.6)		
Unknown	94							
<b>Neoadjuvant chemotherapy, n (%)</b>							<0.001 <sup>c</sup>	
None	1216 (84.7)	209 (92.5)	335 (88.4)	259 (84.9)	272 (82.8)	139 (71.6)		
Yes	219 (15.3)	17 (7.5)	44 (11.6)	46 (15.1)	57 (17.2)	55 (28.4)		
<b>Adjuvant chemotherapy, n (%)</b>							0.879	—
None	442 (30.8)	75 (33.2)	114 (30.1)	89 (29.2)	102 (30.9)	62 (32)		
Yes	992 (69.2)	151 (66.8)	265 (69.9)	216 (70.8)	228 (69.1)	132 (68.0)		
Unknown	1							
<b>Hormonal therapy, n (%)</b>							0.129	—
None	492 (38.1)	83 (39.9)	125 (35.8)	98 (34.9)	109 (38.1)	77 (46.4)		
Yes	798 (61.9)	125 (60.1)	224 (64.2)	183 (65.1)	177 (61.9)	89 (53.6)		
Unknown	145							

Abbreviations: BCS = breast-conserving surgery; CI = confidence interval; HER2 = Human epidermal growth factor receptor 2; NLR = neutrophil-lymphocyte ratio; PLR = platelet-lymphocyte ratio; PR = progesterone receptor.

<sup>a</sup>Derived using the  $\chi^2$ -test for categorical variables, and Kruskal-Wallis test for continuous variables.

<sup>b</sup>Derived using a multivariable logistic regression model on imputed data (using cutoff for NLR = 4.00), showing pooled odds ratios adjusted for age, race, tumour size, lymph node involvement, distant metastasis, grade, lymphovascular invasion, oestrogen receptor status, progesterone receptor status, HER2 status, and NLR.

<sup>c</sup>Statistically significant.

<sup>d</sup>Tumour size unknown in 86 patients.

**Table 2. Demographic, tumour and treatment characteristics of 1435 women with breast cancer by quintiles of pre-treatment platelet-lymphocyte ratio**

	Overall	Quintile 1 PLR ≤100 n=287	Quintile 2 100<PLR ≤129 n=287	Quintile 3 129<PLR ≤161 n=287	Quintile 4 161<PLR ≤215 n=287	Quintile 5 PLR >215 n=287	P <sup>a</sup>	Multivariable odds ratio <sup>b</sup> (95% CI)
Age (years), median	52	56	52	51	50	49	<0.001 <sup>c</sup>	1.00 (0.99–1.01)
<b>Race, n (%)</b>							<0.001 <sup>c</sup>	
Chinese	830 (57.8)	117 (40.8)	150 (52.3)	185 (64.5)	193 (67.2)	185 (64.5)		1.00
Malay	363 (25.3)	75 (26.1)	84 (29.3)	69 (24.0)	63 (22.0)	72 (25.1)		0.64 (0.45–0.91) <sup>c</sup>
Indian	222 (15.5)	89 (31.0)	49 (17.1)	32 (11.1)	28 (9.8)	24 (8.4)		0.41 (0.26–0.66) <sup>c</sup>
Others	20 (1.4)	6 (2.1)	4 (1.4)	1 (0.3)	3 (1.0)	6 (2.1)		1.77 (0.60–5.22)
Tumour size (cm) <sup>d</sup> , median	3.5	3.0	3.0	3.0	3.5	5.0	<0.001 <sup>c</sup>	0.99 (0.95–1.03)
<b>No. of positive axillary lymph nodes, n (%)</b>							0.091	
0	639 (51.7)	141 (55.1)	148 (57.1)	149 (55.2)	114 (46.7)	87 (42.2)		1.00
1–3	285 (23.1)	57 (22.3)	54 (20.8)	63 (23.3)	56 (23.0)	55 (26.7)		1.20 (0.82–1.75)
4–9	170 (13.8)	33 (12.9)	34 (13.1)	29 (10.7)	40 (16.4)	34 (16.5)		1.55 (0.98–2.46)
≥10	141 (11.4)	25 (9.8)	23 (8.9)	29 (10.7)	34 (13.9)	30 (14.6)		1.74 (1.04–2.92) <sup>c</sup>
Unknown	200							
<b>Distant metastasis, n (%)</b>							<0.001 <sup>c</sup>	
None	1222 (86.1)	263 (92.3)	257 (89.5)	259 (91.5)	242 (85.5)	201 (71.5)		1.00
Present	197 (13.9)	22 (7.7)	30 (10.5)	24 (8.5)	41 (14.5)	80 (28.5)		1.77 (1.09–2.86) <sup>c</sup>
Unknown	16							
<b>Grade, n (%)</b>							0.600	
1	83 (7.7)	21 (9.8)	18 (8.1)	20 (9.0)	14 (6.4)	10 (5.2)		1.00
2	514 (4.8)	106 (49.3)	106 (48.0)	97 (43.7)	105 (47.9)	100 (51.5)		1.80 (0.92–3.53)
3	474 (44.3)	88 (40.9)	97 (43.9)	105 (47.3)	100 (45.7)	84 (43.3)		1.40 (0.68–2.88)
Unknown	364							
<b>Lymphovascular invasion, n (%)</b>							0.059	
None	552 (53.4)	124 (56.1)	127 (58.0)	113 (52.1)	111 (55.0)	77 (44.0)		1.00
Present	482 (46.6)	97 (43.9)	92 (42.0)	104 (47.9)	91 (45.0)	98 (56.0)		1.08 (0.73–1.59)
Unknown	401							
<b>Oestrogen receptor status, n (%)</b>							0.109	
Negative	612 (44.9)	110 (40.0)	140 (50.2)	116 (41.6)	124 (46.1)	122 (46.7)		1.00
Positive	751 (55.1)	165 (60.0)	139 (49.8)	163 (58.4)	145 (53.9)	139 (53.3)		0.80 (0.53–1.19)
Unknown	72							
<b>Progesterone receptor status, n (%)</b>							0.257	
Negative	617 (51.2)	119 (48.4)	141 (56.2)	119 (47.2)	122 (51.3)	116 (53.5)		1.00
Positive	587 (48.8)	127 (51.6)	110 (43.8)	133 (52.8)	116 (48.7)	101 (46.5)		1.30 (0.86–1.96)
Unknown	231							
<b>HER2 status, n (%)</b>							0.007 <sup>c</sup>	
Negative	699 (55.1)	151 (57.9)	151 (57.6)	165 (63.2)	120 (47.6)	112 (48.3)		1.00
Positive	456 (36.0)	85 (32.6)	94 (35.9)	78 (29.9)	103 (40.9)	96 (41.4)		1.09 (0.78–1.52)
Equivocal	113 (8.9)	25 (9.6)	17 (6.5)	18 (6.9)	29 (11.5)	24 (10.3)		0.89 (0.50–1.60)
Unknown	167							
NLR (median)	2.20	1.50	1.84	2.18	2.56	3.95	<0.001 <sup>c</sup>	2.23 (1.91–2.62) <sup>c</sup>
<b>Surgery, n (%)</b>							<0.001 <sup>c</sup>	—
None	164 (11.4)	24 (8.4)	23 (8.0)	14 (4.9)	34 (11.8)	69 (24.0)		
Mastectomy	989 (68.9)	194 (67.6)	192 (66.9)	215 (74.9)	209 (72.8)	179 (62.4)		
BCS	282 (19.7)	69 (24.0)	72 (25.1)	58 (20.2)	44 (15.3)	39 (13.6)		
<b>Radiotherapy, n (%)</b>							0.555	—
Yes	835 (62.3)	169 (62.4)	168 (61.1)	179 (66.5)	159 (59.8)	160 (61.5)		
None	506 (37.7)	102 (37.6)	107 (38.9)	90 (33.5)	107 (40.2)	100 (38.5)		
Unknown	94							
<b>Neoadjuvant chemotherapy, n (%)</b>							<0.001 <sup>c</sup>	—
None	1216 (84.7)	260 (90.6)	253 (88.2)	254 (88.5)	236 (82.2)	213 (74.2)		
Yes	219 (15.3)	27 (9.4)	34 (11.8)	33 (11.5)	51 (17.8)	74 (25.8)		
<b>Adjuvant chemotherapy, n (%)</b>							0.316	—
None	442 (30.8)	103 (35.9)	89 (31.0)	84 (29.3)	82 (28.7)	84 (29.3)		
Yes	992 (69.2)	184 (64.1)	198 (69.0)	203 (70.7)	204 (71.3)	203 (70.7)		
Unknown	1							
<b>Hormone therapy, n (%)</b>							0.173	—
None	492 (38.1)	92 (34.7)	105 (40.1)	87 (33.5)	104 (40.9)	104 (41.8)		
Yes	798 (61.9)	173 (65.3)	157 (59.9)	173 (66.5)	150 (59.1)	145 (58.2)		
Unknown	145							

Abbreviations: BCS = breast-conserving surgery; CI = confidence interval; HER2 = Human epidermal growth factor receptor 2; NLR = neutrophil-lymphocyte ratio; PLR = platelet-lymphocyte ratio.

<sup>a</sup>Derived using the  $\chi^2$ -test for categorical variables, and Kruskal-Wallis test for continuous variables.

<sup>b</sup>Derived using a multivariable logistic regression model on imputed data (using cutoff for PLR = 185), showing pooled odds ratios adjusted for age, race, tumour size, lymph node involvement, distant metastasis, grade, lymphovascular invasion, oestrogen receptor status, progesterone receptor status, HER2 status, and NLR.

<sup>c</sup>Statistically significant.

<sup>d</sup>Tumour size unknown in 86 patients.

cutoff values from other cohort studies (Levine *et al*, 1991). We therefore performed sensitivity analyses using dichotomous categorisation of the NLR/PLR, adopting previously reported cutoff values (Krenn-Pilko *et al*, 2014; Templeton *et al*, 2014a,b). On the basis of our findings, it seems that a cutoff value of 4.00 for the NLR (Dirican *et al*, 2014; Templeton *et al*, 2014b), which was also the cutoff value for patients in quintile 5 in this study, is able to distinguish between those with a higher risk of mortality and those with a lower risk. Nevertheless, the HRs for all-cause mortality in previous breast cancer-specific studies were higher than the observed HR in this study (Azab *et al*, 2012, 2013; Noh *et al*, 2013; Dirican *et al*, 2014; Nakano *et al*, 2014). A more recent study, however, did not find an association between NLR and disease-free survival, as well as overall survival (Cihan *et al*, 2014).

Although a previous study had shown that PLR was not associated with either disease-free survival or overall survival in women with breast cancer (Cihan *et al*, 2014), our finding that PLR was an adverse prognostic predictor in breast cancer (using a cutoff value of 185) corroborates the findings of Azab *et al* (2013). As in the analysis of the NLR, the HR of mortality in this previous study was substantially higher than in our current analysis (2.68, 95% CI: 1.61–4.46 vs 1.25, 95% CI: 1.04–1.52). Another recent study, which had used a cutoff value of 292, had also shown that the HR for all-cause mortality was higher than in our study (1.92, 95%

CI: 1.01–3.67 vs 1.30, 95% CI: 0.98–1.70) (Krenn-Pilko *et al*, 2014). However, it is felt that a high cutoff point may miss a substantial number of patients in clinical practice, given that <10% of patients in the current study were grouped into a PLR >292.

The prognostic impact of the NLR and PLR (as reflected by the HR) that we have observed is lower than in previous breast cancer-specific studies, and may be explained by several factors. Given that both the NLR and PLR were mutually correlated, and independently associated with survival, it is important that they are adjusted against each other in the multivariable analysis. It was less clear whether this was done in other studies except in one (Azab *et al*, 2013). Furthermore, patients with an increased NLR/PLR were more likely to be associated with advanced disease stages, and unfavourable tumour characteristics. It is hence plausible that treatment patterns may also vary across the categories, as observed in our study. Only two of the six previous breast cancer-specific studies adjusted for adjuvant radiotherapy or chemotherapy (Azab *et al*, 2012; Dirican *et al*, 2014). Therefore, it remains possible that the higher HRs in the previous studies may be attenuated after adjustment for full treatment details.

Although previous studies had found that the impact of NLR/PLR on breast cancer prognosis varies according to breast cancer subtypes (Noh *et al*, 2013; Krenn-Pilko *et al*, 2014), we did not

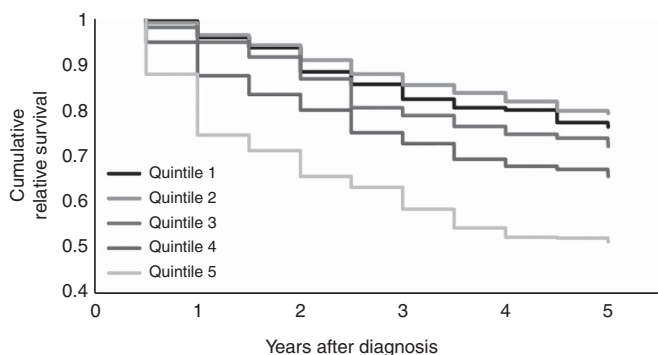


Figure 1. Cumulative relative survival ratio by quintiles of neutrophil-lymphocyte ratio in 1435 Asian women with breast cancer.

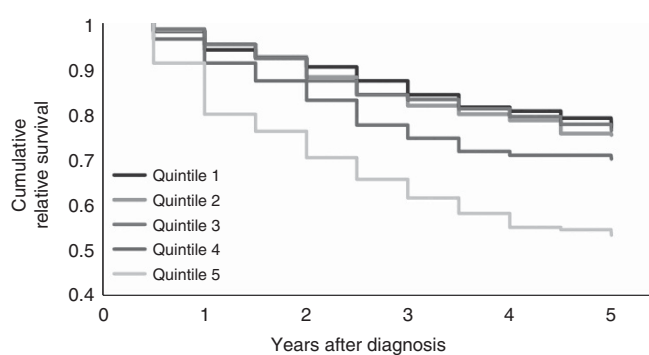


Figure 2. Cumulative relative survival ratio by quintiles of platelet-lymphocyte ratio in 1435 Asian women with breast cancer.

**Table 3. Association between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio, and mortality in 1435 Asian breast cancer patients**

	Total	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P <sub>trend</sub> <sup>a</sup>
<b>Neutrophil-lymphocyte ratio, median</b>	2.20	1.17	1.70	2.26	3.14	5.64	
No. of patients	1435	226	379	305	331	194	
No. of deaths	599	75	135	113	158	118	
5-Year relative survival (95% CI) <sup>b</sup>		76.4 (69.6–82.1)	79.4 (74.4–83.7)	72.1 (66.3–77.3)	65.6 (59.8–70.8)	51.1 (43.3–58.5)	
Crude hazard ratio (95% CI)		1.00	1.06 (0.80–1.41)	1.17 (0.87–1.56)	1.59 (1.21–2.10) <sup>c</sup>	2.56 (1.91–3.42) <sup>c</sup>	<0.001 <sup>c</sup>
Adjusted hazard ratio (95% CI) <sup>d</sup>		1.00	1.03 (0.77–1.39)	1.04 (0.77–1.41)	1.27 (0.95–1.70)	1.50 (1.08–1.63) <sup>c</sup>	0.004 <sup>c</sup>
<b>Platelet-lymphocyte ratio, median</b>	144.2	83.9	114.8	144.2	182.9	286.0	
No. of patients	1435	287	287	287	287	287	
No. of deaths	599	112	98	101	127	161	
5-Year relative survival (95% CI) <sup>b</sup>		77.0 (70.9–82.2)	75.3 (69.4–80.5)	76.3 (70.4–81.4)	70.0 (64.0–75.4)	53.2 (46.9–59.2)	
Crude hazard ratio (95% CI)		1.00	0.87 (0.67–1.15)	0.89 (0.68–1.16)	0.89 (0.68–1.16)	1.82 (1.43–2.31) <sup>c</sup>	0.001 <sup>c</sup>
Adjusted hazard ratio (95% CI) <sup>e</sup>		1.00	0.82 (0.62–1.09)	0.87 (0.65–1.17)	0.92 (0.69–1.22)	1.07 (0.81–1.41)	0.376

Abbreviation: CI = confidence interval.

<sup>a</sup>P for trend is computed by entering the quintiles as a continuous term (score variable: 0, 1, 2, 3, 4) in the Cox model.

<sup>b</sup>Derived using the Ederer II method; ratio of observed survival in women with breast cancer to the survival that would have been expected for the women of the general population, which is matched for age. Expected survival was derived from the Malaysian life table.

<sup>c</sup>Statistically significant.

<sup>d</sup>Derived using Cox regression adjusted for age at diagnosis, ethnicity, tumour size, number of positive axillary lymph nodes, distant metastasis, oestrogen/progesterone receptor status, HER2 status, tumour grade, lymphovascular invasion, type of surgery, radiotherapy, neoadjuvant chemotherapy, adjuvant chemotherapy regime, hormone therapy and platelet-lymphocyte ratio.

<sup>e</sup>Similar as model 3, but now adjusted for neutrophil-lymphocyte ratio.

find significant effect modification. Furthermore, our results are not entirely in agreement with previous studies. We are hence uncertain whether our significant results were due to multiple testing.

The mechanism by which the NLR and PLR may impact breast cancer prognosis remains unclear. The peripheral NLR and PLR are thought to be proxies of the on-going inflammatory process in the tumour microenvironment. A complex body of scientific evidence suggests that neutrophils and platelets are associated with pro-tumour activities *in vivo* such as enhanced angiogenesis, which contribute to tumour cell proliferation and promote metastatic potential of the tumour cells (Coussens and Werb, 2002; De Larco *et al*, 2004; Bambace and Holmes, 2011; Voutsadakis, 2014).

Lymphocytes, on the other hand, have been implicated in having an important role in cancer immune surveillance, and are hypothesised to suppress tumour maturation (Shankaran *et al*, 2001). An increased concentration of intratumoral CD8<sup>+</sup> cytotoxic lymphocytes in breast cancer has been strongly associated with decreased recurrence, and higher survival outcomes (Mahmoud *et al*, 2011). It is hence biologically plausible that imbalances in the ratio of the peripheral neutrophils/platelets to lymphocytes may provide an insight into underlying tumour progression and prognosis in individuals with breast cancer. This seems to further suggest that the NLR and PLR may also have the potential to be predictive markers in breast cancer.

To our knowledge, this is the largest study to have investigated the prognostic role of the pre-treatment NLR/PLR in an unselected cohort of women with breast cancer, of which a high proportion of patients (~70%) had available information on the NLR/PLR. A major strength of this study is that we had detailed information on tumour characteristics and treatment, allowing for extensive confounder adjustment. Although we did not have information on the cause of death in our Registry, we had estimated RSRs, which provide an estimate of net survival attributed to breast cancer, given that it captures both the direct and indirect contribution of cancer diagnosis on survival (Coleman *et al*, 2008). However, (relative) survival may have been slightly overestimated in the current study, as breast cancer is more common in affluent women (Clarke *et al*, 2002), making life expectancies between the patients and the background population not entirely comparable. Given that we had compared all-cause mortality in the multivariable analysis, it is acknowledged that lack of data on patients' comorbidities may have affected our study results.

**Table 4. Association between neutrophil–lymphocyte ratio/platelet–lymphocyte ratio, and mortality in 1435 Asian breast cancer patients using different cutoff values**

	Number of patients	Hazard ratio (95% CI) <sup>a</sup>
<b>Neutrophil–lymphocyte ratio</b>		
≤ 3.00	1045	1.00
> 3.00	390	1.20 (0.99–1.45)
≤ 4.00	1241	1.00
> 4.00	194	1.37 (1.08–1.74) <sup>b</sup>
≤ 5.00	1316	1.00
> 5.00	119	1.45 (1.08–1.93) <sup>b</sup>
<b>Platelet–lymphocyte ratio</b>		
≤ 185	1011	1.00
> 185	424	1.25 (1.04–1.52) <sup>b</sup>
≤ 292	1302	1.00
> 292	133	1.30 (0.98–1.70)

Abbreviations: CI = confidence interval; HER2 = Human epidermal growth factor receptor 2; NLR = neutrophil–lymphocyte ratio; PLR = platelet–lymphocyte ratio.  
<sup>a</sup>Hazard ratios for NLR were derived using Cox regression adjusted for age at diagnosis, ethnicity, tumour size, number of positive axillary lymph nodes, distant metastasis, oestrogen/progesterone receptor status, HER2 status, tumour grade, lymphovascular invasion, type of surgery, radiotherapy, neoadjuvant chemotherapy, adjuvant chemotherapy regime, hormone therapy and platelet–lymphocyte ratio. For PLR, a similar Cox model was used, but was instead adjusted for neutrophil–lymphocyte ratio.  
<sup>b</sup>Statistically significant.

**CONCLUSION**

In conclusion, our results support the findings of previous studies that an increased NLR and PLR are independently associated with a higher risk of all-cause mortality in women with breast cancer. This association does not seem to be modified by the subtype of

**Table 5. Association between neutrophil–lymphocyte ratio/platelet–lymphocyte ratio and mortality in 1101 Asian breast cancer patients by breast cancer subtype**

	Neutrophil–lymphocyte ratio		Platelet–lymphocyte ratio	
	≤ 4.00 (n = 975)	> 4.00 (n = 126)	≤ 185 (n = 801)	> 185 (n = 300)
<b>ER + or PR + and HER2 – (n = 470)</b>				
Adjusted hazard ratio (95% CI) <sup>a</sup>	1.00	1.16 (0.61–2.21)	1.00	1.21 (0.80–1.85)
<b>ER + or PR + and HER2 + (n = 216)</b>				
Adjusted hazard ratio (95% CI) <sup>b</sup>	1.00	1.14 (0.65–1.99)	1.00	2.01 (1.23–3.29) <sup>c</sup>
<b>ER – and PR – and HER2 + (n = 207)</b>				
Adjusted hazard ratio (95% CI) <sup>d</sup>	1.00	1.63 (1.04–2.55) <sup>c</sup>	1.00	0.92 (0.60–1.41)
<b>ER – and PR – and HER2 – (n = 208)</b>				
Adjusted hazard ratio (95% CI) <sup>e</sup>	1.00	1.91 (1.00–3.65) <sup>c</sup>	1.00	1.27 (0.76–2.14) <sup>c</sup>

Abbreviations: CI = confidence interval; ER = oestrogen receptor; HER2 = Human epidermal growth factor receptor 2; NLR = neutrophil–lymphocyte ratio; PLR = platelet–lymphocyte ratio; PR = progesterone receptor. Patients with unknown ER, PR or HER2 status, as well as those with equivocal HER2 status without fluorescence *in situ* hybridisation were excluded. Adjusted hazard ratios were derived using the Cox regression model. Only factors that changed the hazard ratios for NLR > 4.0/PLR > 185 by more than 10% in the initial bivariable analyses were included in the final multivariable models.  
<sup>a</sup>For NLR, the final model was adjusted for race, tumour size, number of positive axillary lymph nodes, distant metastasis, type of surgery, neoadjuvant chemotherapy, and platelet–lymphocyte ratio. For PLR, the final model was adjusted for tumour size, number of positive axillary lymph nodes, distant metastasis, type of surgery, neoadjuvant chemotherapy, and neutrophil–lymphocyte ratio.  
<sup>b</sup>For NLR, the final model was adjusted for tumour size, number of positive axillary lymph nodes, distant metastasis, type of surgery, neoadjuvant chemotherapy, and platelet–lymphocyte ratio. For PLR, the final model was adjusted for age at diagnosis, race, tumour size, number of positive axillary lymph nodes, distant metastasis, and neutrophil–lymphocyte ratio.  
<sup>c</sup>Statistically significant.  
<sup>d</sup>For NLR, the final model was adjusted for tumour size, number of positive axillary lymph nodes, distant metastasis, type of surgery, neoadjuvant chemotherapy, and platelet–lymphocyte ratio. For PLR, the final model was adjusted for tumour size, number of positive axillary lymph nodes, distant metastasis, type of surgery, neoadjuvant chemotherapy, and platelet–lymphocyte ratio.  
<sup>e</sup>For NLR, the final model was adjusted for number of positive axillary lymph nodes, type of surgery, neoadjuvant chemotherapy, and platelet–lymphocyte ratio. For PLR, the final model was adjusted for distant metastasis, type of surgery, neoadjuvant chemotherapy, and platelet–lymphocyte ratio.

breast cancer. Given that the NLR and PLR are readily available biomarkers in clinical settings, future prognostic studies are warranted to determine the added value of these biomarkers to existing prognostic indicators of breast cancer that are routinely used in clinical practice, and also on their potential as predictive markers in breast cancer.

## ACKNOWLEDGEMENTS

This study was financially supported by the Ministry of Education Malaysia (High Impact Research Grant (UM.C/HIR/MOHE/06)).

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DISCLAIMER

The funder did not have any role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

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