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Research Article

Are Inflammatory Markers Significant Prognostic Factors for Head and Neck Cancer Patients?

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Keywords
Platelet/lymphocyte ratio · Neutrophil/lymphocyte ratio · Head and neck cancer · Survival

Abstract
Introduction: Recent studies have reported that elevated levels of platelets and inflammatory markers are associated with poor treatment outcomes among patients with solid tumours, but reports are conflicting in head and neck cancer (HNC) patients. ***Objective:*** To establish if pre-treatment anti-inflammatory markers can be used as a prognostic tool of overall survival and tumour control among HNC patients. ***Methods:*** We retrospectively reviewed the pre-treatment platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) of 147 HNC patients from 2014 to 2018 and analysed their association with tumour progression and overall treatment outcomes. The optimal cut-off was established at >200 for high PLR and >2.85 for high NLR. ***Results:*** After adjusting for age, disease stage, and treatment, patients with higher PLR had an almost 3 times higher risk of mortality during the study period than patients with normal PLR (hazard ratio [HR] 2.79, 95% confidence interval [CI] 1.43–5.47, $p < 0.01$). Furthermore, the patients with higher NLR had an >2.5 times higher risk of mortality than those with normal NLR (HR 2.62, 95% CI 1.19–5.81, $p = 0.02$). ***Conclusion:*** This observational study shows that elevated PLR and NLR in HNC patients, who were treated with either surgery or primarily chemoradiotherapy, are associated with poor overall survival.

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Introduction

The German pathologist Rudolf Virchow first proposed an association between cancer and inflammation in 1863, as he observed that pathological tumours were always accompanied by inflammatory cells, but his theory did not gain much attention until the century that followed [1]. The past 2 decades, however, showed convincing evidence of cancer-related inflammation from epidemiological data to molecular studies in animal models [2]. Chronic inflammatory disease, either from microbial infection or autoimmune disease, is now known as major risk factor for the development of some solid organ cancers. *Helicobacter pylori*, for example, is highly correlated to the development of stomach cancer and gastric mucosal lymphoma. Head and neck carcinoma (HNC) is related to constant inflammation from tobacco use, alcohol intake, and human papillomavirus [3].

Recent studies have reported associations between pre-treatment serum inflammatory markers and patients' overall survival in several types of cancer, such as pancreas [4], skin [5], stomach [6], oesophagus [7], colon [8], bladder [9], and ovarian cancer [10]. Beyond the haemostatic role of blood-circulating platelets, they produce growth factors and cytokines that are involved in tumour formation, angiogenesis, and metastasis in colorectal cancer [11, 12]. Neutrophils and lymphocytes were also reported as markers for overall survival in cholangiocarcinoma [13]. Tumour-associated neutrophils promote carcinogenesis, tumour progression, and metastatic spread [14], while lymphocytes, on the other hand, repress tumour formation by inducing cytotoxic cell death [15]. However, some reports are conflicting, especially in head and neck malignancies. In 2018, Chen et al. [16] reported that pre-operative platelet level and inflammatory markers like lymphocytes failed to be independent prognostic markers among patients with laryngeal squamous cell carcinoma. In 2017, Sumner et al. [17] reported that lymphocyte levels have no impact on survival or tumour control in head and neck squamous cell carcinoma patients.

In this study, we wanted to establish the role of inflammatory markers, specifically the platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR), as prognostic markers for overall survival of HNC patients treated in a district hospital in Wales. Given that these data are readily available from pre-treatment routine blood tests, PLR and NLR could give an overview on risk stratification for survival prediction.

Materials and Methods

Following approval from the local ethics committee, data on new HNC cases seen at the Hywel Dda University Health Board (Wales, UK) from November 2014 to November 2018 were retrieved from the Data for Head and Neck Oncology System (DAHNOS). Patients <18 years old, with thyroid carcinoma, or with skin malignancies were excluded. A total of 172 patients were identified, and data including age, gender, site and size of the primary pathological tumour (T), neck involvement and size (N), distant metastasis (M), TNM staging based on updated AJCC TNM scoring at the time of diagnosis, inflammatory markers from blood tests taken 6 weeks before initiation of treatment, specifically neutrophil and lymphocyte counts, platelet levels, CRP, co-morbidities, especially ongoing infections, date of diagnosis, multidisciplinary team recommendation, date and mode of initial treatment, findings on follow-up (i.e., disease-free survival or recurrence), and mortalities were collected. Among these, 20 with a poor survival were excluded; they had either far advanced disease or presented ongoing significant medical co-morbidities, and a multidisciplinary team suggested palliative treatment. Furthermore, 5 were excluded for incomplete follow-up data as they were transferred to a different treatment centre, leaving 147 patients for analysis.

The primary outcome measure was to evaluate the effect of the platelet/lymphocyte ratio (PLR) and the neutrophil/lymphocyte ratio (NLR) on survival after adjusting for TNM stage, age, and treatment. Inflammatory levels, specifically neutrophils, lymphocytes, and platelet levels, were collected from routine full blood counts prior to initiation of treatment. There are various cut-off levels mentioned in the literature

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Table 1. Characteristics and treatment outcome of 147 patients with head and neck cancer

Mean age (range), years		66.2 (37–89)
Site		
	Oral cavity	3 (2.0%)
	Oropharynx	55 (37.4%)
	Larynx	54 (36.7%)
	Hypopharynx	11 (7.5%)
	Paranasal sinus	8 (5.5%)
	Nasopharynx	2 (1.4%)
	Salivary gland	11 (7.5%)
	Neck (unknown primary)	1 (0.7%)
Neck involvement		
	N0	82 (55.8%)
	N1	11 (7.5%)
	N2a	4 (2.8%)
	N2b	37 (25.2%)
	N2c	11 (7.5%)
	N3	2 (1.4%)
Metastasis		
	M0	143 (97.3%)
	M1	4 (2.7%)
AJCC grade		
	Stage 1	27 (18.3%)
	Stage 2	17 (11.6%)
	Stage 3	17 (11.6%)
	Stage 4	86 (58.5%)
Treatment		
	Surgery ± chemo-/ radiotherapy	50 (34%)
	Chemo- ± radiotherapy	97 (66%)
Recurrence		
	Yes	23 (15.6%)
	No	124 (84.4%)
Death		
	Yes	38 (25.9%)
	No	109 (74.1%)
Survival rate, %		
	1 year	82
	2 years	69
	3 years	53

n (%) of patients are shown unless indicated otherwise.

regarding elevated NLR (range: 2.23–3.5 [18–20]) and PLR (range: 128.3–322.0 [21]). The optimal cut-off values for this study were calculated using Harrell's C, which is a measure of concordance and is similar to the area under the receiver-operating characteristics curve used by other authors.

Kaplan-Meier survival analyses were used to assess the univariate effect of the ratios on survival. Cox proportional hazards model was used to assess the multivariate effect of the ratios on survival. Univariate Cox proportional hazards models were used to assess stage, age, and treatment covariates for the saturated multivariate model though not for the purposes of reducing the model. The saturated models were assessed for proportionality. The specification and proportionality of the saturated models were assessed using formal tests. All analyses were conducted in Stata IC 15.1.

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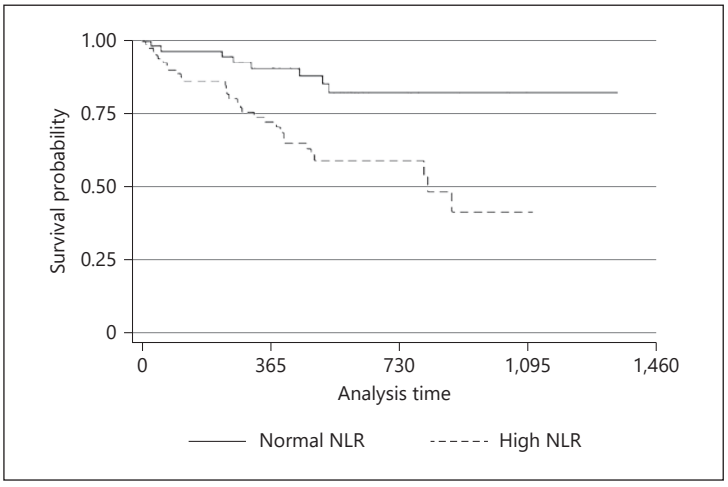

Fig. 1. Kaplan-Meier analysis showing patients with normal neutrophil/lymphocyte ratio (NLR) had higher overall survival probability compared to patients with NLR >2.75.

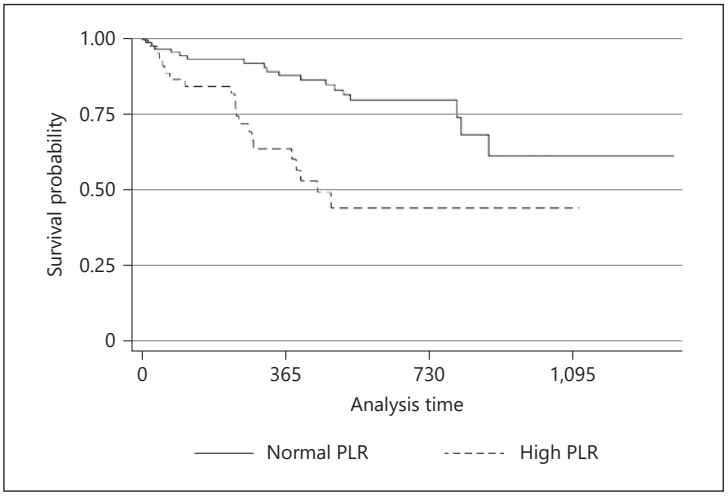

Fig. 2. Kaplan-Meier analysis showing patients with normal platelet/lymphocyte ratio (PLR) had higher overall survival probability compared to patients with PLR >200.

Results

A total of 147 patients were included in this study. Among these, 34% (50 patients) had primarily surgical treatment (with or without subsequent chemo-/radiotherapy) and 66% (98 patients) had chemo-/radiotherapy or non-surgical treatment (Table 1). Their mean age was 66.2 years (range 37–89 years). The median follow-up was 15.1 months. The 1-, 2-, and 3-year overall survival rates were 82, 69, and 53%, respectively. The mortality rate was 25.9% (38 deaths), while the recurrence rate was 15.6% (n = 23).

The PLR and NLR cut-offs were determined on the basis of a review of the literature and assessments of Harrell's C. The final models correctly identified 74% of cases for the NLR cut-off of 2.85 and 75% of cases for the PLR cut-off of 200.

Among the 147 patients, 46 had PLR ≥200 and 101 had <200. There were 85 patients who had NLR ≥2.85 and 62 <2.85. There was a statistically significant association between higher ratios and later stages for PLR (Fisher's exact test p = 0.003) and a marginally non-significant association for NLR (Fisher's exact test p = 0.07).

Kaplan-Meier analysis showed that patients with normal NLR had higher overall survival probability than patients with NLR >2.75 (Fig. 1). Likewise, patients with normal PLR had higher overall survival probability than patients with PLR >200 (Fig. 2). The 1-, 2-, and 3-year

Table 2. Univariate analysis showing independent predictors of overall survival were advanced stage, age, and high NLR and PLR

Variable	Level	HR	95% CI	*p* value
Stage	I/II (baseline)	–	–	–
	III/IV	2.98	1.16–7.64	**0.02**
Treatment	Surgery (baseline)	–	–	–
	Non-surgical	1.43	0.69–2.95	0.33
Age	Per year increase	1.03	1.00–1.07	**0.04**
NLR	Normal ratio	–	–	–
	High ratio	3.22	1.48–7.05	**<0.01**
PLR	Normal ratio	–	–	–
	High ratio	3.23	1.69–6.16	**<0.01**

Table 3. Adjusted HR showing patients with higher PLR were almost 3 times more likely to die during the study period than patients with normal PLR

Variable	Level	HR	95% CI	*p* value
PLR	Normal ratio	–	–	–
	High ratio	2.79	1.43–5.47	**<0.01**
Stage	I/II (baseline)	–	–	–
	III/IV	4.04	1.49–10.97	**<0.01**
Treatment	Surgery (baseline)	–	–	–
	Non-surgical	1.59	0.77–3.29	0.21
Age	Per year increase	1.06	1.02–1.09	**<0.01**

survival rates of those who had normal PLR were 88, 78, and 57%, while they were 67, 47, and 47% of those who had high PLR (>200), respectively.

Univariate analysis showed that the independent predictors of overall survival were advanced stage of disease (stage III/IV) ($p = 0.02$), age ($p = 0.04$), high NLR ($p < 0.01$), and high PLR ($p < 0.01$). The type of treatment, either surgical or non-surgical, was not a predictor of overall survival ($p = 0.33$) (Table 2).

After adjusting for age, stage, and treatment, patients with higher PLR had an almost 3 times higher risk of mortality during the study period than patients with normal PLR (hazard ratio [HR]2.79, 95% confidence interval [CI] 1.43–5.47, $p < 0.01$) (Table 3).

After adjusting for age, stage, and treatment, patients with higher NLR had an >2.5 times higher risk of mortality during the study period than patients with normal NLR (HR 2.62, 95% CI 1.19–5.81, $p = 0.02$) (Table 4).

The PLR (likelihood ratio test result $\chi^2 = 8.91$, $p < 0.01$) and the NLR ($\chi^2 = 6.58$, $p = 0.02$) were found to outperform lymphocyte counts as a linear term ($\chi^2 = 0.10$, $p = 0.75$) with regard to improving the adequacy of the model containing stage, treatment, and age. Lymphocyte count as a quadratic term yielded a similar likelihood ratio test to those of the ratios ($\chi^2 = 7.83$, $p = 0.02$) but exhibited to a turning point outside of the normal range (6.1) and deviations in the goodness of fit plots. Lymphocyte counts as fractional polynomials

Table 4. Adjusted HR showing patients with higher NLR were >2.5 times more likely to die during the study period than patients with normal NLR

Variable	Level	HR	95% CI	*p* value
NLR	Normal ratio	–	–	–
	High ratio	2.62	1.19–5.81	**0.02**
Stage	I/II (baseline)	–	–	–
	III/IV	4.34	1.63–11.54	**<0.01**
Treatment	Surgery (baseline)	–	–	–
	Non-surgical	1.46	0.70–3.03	0.32
Age	Per year increase	1.05	1.02–1.09	**<0.01**

Table 5. Some known associations between cancer and inflammation

Organ involved in malignancy	Inflammatory triggers
Oropharynx	Human papillomavirus
Nasopharynx	Epstein-Barr virus
Paranasal sinus	Dusts from nickel, chromium, wood, leather
Oral cavity	Betel quid, areca nut
Cervix	Human papilloma virus
Stomach	*Helicobacter pylori*
Lungs	Smoking, asbestos, silica
Bladder	Schistosomiasis
Ovary	Pelvic ulcer disease, talc
Liver	Hepatitis B and C virus
Colon	Inflammatory bowel disease

were dropped by the automated model fitting process as they did not improve the deviance of the base model.

The test of the proportional hazard assumption was satisfactory for both the platelet (p = 0.77) and neutrophil models (p = 0.76). Visual inspection of plots did not suggest any violation of the proportionality assumption. The link tests were satisfactory for both the platelet (p = 0.77) and neutrophil models (0.70), which indicates both models were adequately specified. Visual inspection of Nelson-Aalen plots for both models did not indicate any lack of goodness of fit for either model.

Discussion/Conclusion

The past 3 decades saw emergence of great interest in establishing links between inflammation and carcinogenesis [1]. Chronic inflammation caused by infectious, chemical, and physical agents, autoimmune diseases, or even due to unknown aetiology is clearly correlated with increased risk of malignancy (Table 5) [1, 3, 22, 23]. In 2012, it was estimated that 15% of global cancer is due to microbial agents [24]. The top 5 infectious agents identified were *H. pylori*, human papillomavirus, hepatitis B virus, hepatitis C virus, and Epstein-Barr virus. Neutrophils, classically known as foot soldiers of the immune system, are essential in mounting an attack to foreign organisms and defending the host from pathogens. They are normally

short-lived and programmed to die around 5 days after entering the blood stream from the bone marrow [25]. However, if this defence mechanism persists a prolonged period of time, releasing inflammatory mediators like cytokines and chemokines, a tumour microenvironment is created which leads to mutation, unregulated proliferation, and metastasis. Pro-inflammatory cytokines like tumour necrosis factor (TNF), induces death of diseased cells, but when secreted chronically, it becomes an endogenous tumour promoter. A large-scale global genetic analysis showed that tumour-associated neutrophils are the most significant adverse prognostic population in pan-cancer analysis [14]. Lymphocytes, on the other hand, are rarely seen in the tumour microenvironment [1], and its presence in the blood is a prognostic sign of a "healthy tumour profile" where these natural killer (NK) cells hinder tumour proliferation, inhibit migration, and destroy metastases [26]. Combining these observations, the NLR has been reported in several clinical studies to be relevant in tumour progression and that a high pre-treatment NLR is an independent prognostic marker of poor overall survival, as seen in our study, both in surgical and non-surgical treatment arms. Conversely, a low pre-treatment NLR predicts good response to radiotherapy or concurrent chemoradiotherapy in uterine cervical squamous cell carcinoma [27].

Platelets are known for their haemostatic functions since Bizzozero noted the behaviour of these anucleated blood cells in 1882 [28]. Platelet disorders include autoimmune thrombocytopaenia, von Willebrand disease, platelet dysfunction in uraemia, and a variety of diseases related to abnormal thrombus formation. Further studies show bidirectional interactions between cancer and platelets: cancer cells induce platelet activation, and activated platelets influence tumour growth, angiogenesis, and metastasis [29]. Several animal studies showed a significant decrease in metastatic activities when platelet count and functions were reduced [30, 31]. Activated platelets contain angiogenesis-controlling cytokines such as VEGF, PDGF, TGF, epidermal growth factors, angiopoietin-1, IGF-1, sphingosine-1-phosphate, and matrix metalloproteinases [29], and experimental studies which target these proteins inhibited tumour growth, cell invasion, angiogenesis, and metastasis [32, 33]. Chemokines CXCL5 and CXCL7 are secreted by platelets when in contact with cancer cells, which in turn attract granulocytes and guide the formation of early metastasis sites [34]. Moreover, cancer cell growth and metastasis were inhibited in platelet-deficient mice [35]. Further analysis revealed the mechanism involves lymphocyte functions, specifically NK cells, as tumour reduction and metastatic inhibition in mice were reversed when NK cell activity was intentionally impaired or depleted [36]. Conversely, when NK cell activity was enhanced in a syngeneic mouse model, adult nude mice were very resistant to metastasis [37]. Both in vitro and in vivo studies show that platelets protect tumour cells from NK lysis via surface shielding, which allows the cancerous cells to escape from immune surveillance [38].

Apart from experimental studies, the association of elevated platelet counts with malignancies has been well described in a clinical setting. In 1964, Levin and Conley [39] reported thrombocytosis in 40% of cases with inoperable solid tumours. Others believe that the elevated platelet count might precede the diagnosis of malignancy [40]. More importantly, thrombocytosis is seen frequently among patients with poor survival and unfavourable response to treatment. Combining this observation with circulating lymphocytes (PLR) provides a stronger prognostic tool in overall survival of cancer patients, as seen in several studies [4–10]. Only a few clinical studies with a small number of patients report the role of platelets in HNC formation [41]. Our study shows that patients who had advanced cancer (stages 3 and 4) had elevated NLR and PLR compared to those in early-stage disease. The patients with low NLR had a higher overall survival rate than the patients with high NLR (>2.75). Likewise, patients with low PLR had a higher overall survival rate than those with high PLR (>200). High pre-treatment NLR and PLR were significantly associated with increased risks of death and cancer progression. Combining the pro-tumour inflammatory

processes associated with neutrophils and anti-tumour activities associated with lymphocytes, especially NK cells, an increased NLR may suggest lower anti-tumour response and increased pro-tumour inflammation. These findings are compatible with other clinical and epidemiological data from cancers arising from various organs. Conversely, a low NLR was seen in patients having complete response to treatment among patients who had radiation therapy and concurrent chemoradiotherapy in uterine cervical cancer [27]. Low NLR and PLR at diagnosis indicated superior overall survival and disease-free survival in patients with diffuse large B-cell lymphoma [42]. Furthermore, our observations are mechanistically consistent with the findings in recent clinical studies on immunotherapy of solid tumours where checkpoint inhibitors such as nivolumab and pembrolizumab reinforce the patient's immune system, specifically T-lymphocyte functions, and resulted in improved overall survival [43].

The strengths of the study are the straightforward data collection from routine pre-operative blood tests, good follow-up rate, and clear documentation of treatment outcome as the patients were regularly followed up for 5 years. The necessary information and data like blood tests, recurrence, and mortality are all available in the hospital's electronic databank and have been double checked by other researchers leaving errors to a minimum. One limitation of the study is being retrospective with a relatively small sample size, and thus we are unable to do a sub-analysis with respect to 4 disease stages or site-specific behaviour without increasing the chance of type 2 error, as the data have been extracted only from 1 district general hospital. This could be addressed by expanding the study on a larger multisite scale to enable sub-group analysis.

In summary, the so-called anti-inflammatory agents have wider use apart from measures of inflammatory responses. We have demonstrated that the PLR and the NLR outperform lymphocyte counts in terms of modelling disease progression. These ratios are also much easier to calculate and much easier to use in practice than the best-fitting lymphocyte count term which takes the quadratic form.

We have shown in this study that HNC patients with higher pre-treatment PLR were almost 3 times more likely to die during the study period than patients with normal PLR. Furthermore, those with higher NLR were >2.5 times more likely to die than patients with normal NLR. These observations were similar to those in other solid organ tumours indicating that PLR and NLR provide a strong prognostic tool in overall survival of cancer patients.

Although further studies with higher sample sizes are needed to validate our findings, this inexpensive yet valuable information from routine pre-treatment blood tests might be useful in survival prediction and tailored therapy.

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Statement of Ethics

The data we used in this study were anonymised, and a full ethics approval for this study was granted by the London-Riverside Research Ethics Committee (REC reference 18/LO/1524; protocol No. SRP 8.2.18; IRAS project ID 234078).

Disclosure Statement

The authors have no conflict of interests to declare.

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Author Contributions

E.A. and V.P. conceived the idea, study design, collected data, performed data analysis, and wrote the paper. G.D. helped with the study design, data analysis (particularly the statistical interpretations), and writing of paper. Y.K. helped with study design, data collection, data analysis, and writing of manuscript.

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