Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(4) 1–15

DOI: 10.1177/03000605211004229
journals.sagepub.com/home/imr

SAGE

The predictive value of pretreatment haemoglobin-to-red cell distribution width ratio for overall survival of patients with advanced non-small cell lung cancer: a propensity score matching analysis

Huiqin Jiang*, Wei Jiang*, Liping Tan, Qitao Yu, Feiwen Liu, Yucong Huang, Jianbo He and Shaozhang Zhou

Abstract

Objective: To investigate the prognostic value of pretreatment haemoglobin-to-red cell distribution width radio (HRR) in predicting overall survival (OS) in patients with advanced non-small cell lung cancer (NSCLC).

Methods: This retrospective study analysed patients with advanced NSCLC. Kaplan–Meier survival analysis and Cox proportional hazards regression analysis were conducted to evaluate the predictive value of HRR for OS. A propensity matching analysis was used to reduce the impact of other confounding factors on the results.

Results: A total of 448 patients were enrolled in the study. The median HRR was 0.984, which was used as the cut-off value. Regardless of matching or not, a lower HRR was correlated with an unfavourable risk of death. After propensity matching, univariate and multivariate analysis showed that HRR was an independent factor for the prognosis of NSCLC (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.17, 2.04; HR 1.57, 95% CI, 1.17, 2.10; respectively). Kaplan–Meier

Department of Respiratory Oncology, Guangxi Cancer Hospital and Guangxi Medical University Affiliated Cancer Hospital, Nanning, Guangxi Zhuang Autonomous Region, China

*Huiqin Jiang, Wei Jiang contributed equally to this work.

Corresponding author:
Shaozhang Zhou, Department of Respiratory Oncology, Guangxi Cancer Hospital and Guangxi Medical University Affiliated Cancer Hospital, 71 Heti Road, 530021, Nanning, Guangxi Zhuang Autonomous Region, China.
Email: zhoushaozhang@gxmu.edu.cn

analysis showed that low HRR was associated with shortened OS. The relationship between HRR and the risk of death was consistent across all patient subgroups after stratification by subgroup analysis.

Conclusions: These findings showed that a lower pretreatment HRR could be a potentially valuable prognostic factor in patients with advanced NSCLC.

Keywords

Non-small cell lung cancer, prognosis, haemoglobin-to-red cell distribution width radio, overall survival, propensity score matching

Date received: 17 February 2021; accepted: 1 March 2021

Introduction

Lung cancer is the most diagnosed cancer worldwide and accounts for 20% of cancer-related deaths.[1] Approximately 80–85% of patients are diagnosed with non-small cell lung cancer (NSCLC).[2] Most of the patients with NSCLC do not get the opportunity to receive radical treatment because their cancer was not discovered early enough.[3] In recent years, the treatment of NSCLC has developed rapidly and targeted therapies and immunotherapy have emerged.[4] It has become more and more common for patients with NSCLC to receive multiple therapies to control their disease.[5] Treatment outcomes remain heterogeneous, with a 5-year survival rate ranging from 4% to 17%.[6]

At present, the TNM staging system has been widely applied to predicting survival and guiding therapeutic regimens in clinical practice.[7,8] However, it appears to be limited in terms of being able to further discriminate the survival of patients with advanced and metastatic disease.[7,8] There is considerable evidence that comprehensive and multidimensional factors determine the clinical outcome of cancer patients.[9–11] Therefore, exploring the prognostic indicators or biomarkers that can be used to predict survival and inform clinical decision-making for cancer patients is extremely important. Blood-based markers with rapid, non-invasive and repeatable features have been shown to have significant advantages in the fields of prediction and prognosis. For example, an association between haematological indicators, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Glasgow prognostic score (GPS) and clinical outcomes have been increasingly identified in a variety of cancer types.[12–20]

The haemoglobin-to-red cell distribution width ratio (HRR) has been shown to be a predictive marker for survival in several malignant diseases.[21–26] Research has demonstrated that a lower HRR is associated with unfavourable clinical outcomes in various cancers, including gastric cancer, head and neck cancer, small cell lung cancer and oesophageal squamous cell carcinoma.[21–24] However, published studies concerning patients with NSCLC are rare.[25,26] Moreover, most of the aforementioned studies did not perform propensity matching to minimize other confounding influences on outcomes.

The present study retrospectively analysed a cohort of patients with advanced, treatment-naïve NSCLC using a propensity score matching approach to investigate the prognostic significance of HRR after adjusting for other potential covariates.

Patients and methods

Patients

This study retrospectively reviewed data from consecutive patients that were initially diagnosed with advanced NSCLC in the Department of Respiratory Oncology, Guangxi Cancer Hospital and Guangxi Medical University Affiliated Cancer Hospital, Nanning, Guangxi Zhuang Autonomous Region, China between June 2009 and August 2018. The inclusion criteria were as follows: (i) pathologically confirmed advanced NSCLC at the initial diagnosis; (ii) clinically diagnosed local advanced (stage IIIB) or metastasis (stage IV); (iii) no history of radiotherapy, immunotherapy, chemotherapy or other treatments before diagnosis; (iv) the availability of complete follow-up data. The exclusion criteria were as follows: (i) pathologically confirmed small cell lung cancer or not otherwise specified at the initial diagnosis; (ii) patients with a history of a second primary malignancy; (iii) stages I–IIIA; (iv) patients with a history of anaemia; (v) patients with infectious, inflammatory or lymphoproliferative diseases.

The study was approved by the Ethics Committee of Guangxi Cancer Hospital and Guangxi Medical University Affiliated Cancer Hospital (no. LW2020062; approval date: 10 October 2020). Due to the retrospective nature of the analysis, informed consent from patients was waived. All patient data were treated with confidentiality. The study was conducted in accordance with the Declaration of Helsinki.

Variables and definition of terms

The patient data were collected from the electronic medical record system of the hospital. HRR was defined as haemoglobin (Hb; g/dl) divided by red cell distribution width (RDW; %). The date from diagnosis of advanced NSCLC to the date of death or last follow-up visit was defined as the overall survival (OS). Follow-up was every 3 months until 31 August 2018. A nonsmoker was defined as a person that smokes no more than 100 cigarettes in their lifetime; and a smoker was defined as a person that had stopped smoking for <1 year or was still a current smoker. The Eastern Cooperative Oncology Group performance status (ECOG-PS) was used to score each patient's physical condition.[27] The pathology was classified according to World Health Organization criteria (3rd version).[28] The cancer staging was determined using the American Joint Committee on Cancer Guidelines (7th version).[29] The GPS was based on serum albumin and C-reactive protein (CRP) scores: 2 points for CRP >10 mg/l and albumin <3.5 g/dl; 1 point for CRP increase or albumin reduction; if none of these abnormalities exist the score was 0 points.[30] NLR was calculated by division of the absolute neutrophil and lymphocyte counts. PLR was calculated by division of the absolute platelet and lymphocyte counts.[31] The median PLR and NLR values were used as the cut-off values.

Statistical analyses

All statistical analyses were performed using the software package R version 3.4.3 (Basics of R Statistical Calculations, Vienna, Austria) and Empower (X&Y Solutions, Boston, MA, USA). To minimize the influence of confounding factors on the outcome, propensity-score matching (PSM) was used balance the clinical characteristics of the two groups. Matching was performed using a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width equal to 0.02 of the standard deviation of the propensity score's logit. Medians and ranges were used to represent continuous variables

and then they were converted to dichotomous variables expressed in frequencies and percentages. If constant variables showed a normal distribution, the comparison used Student's *t*-test. Continuous variables that showed a skewed distribution were compared using Kruskal–Wallis *H*-test. Continuous variables and categorical variables were analysed using Student's *t*-test and Pearson's χ^2-test, respectively. Fisher's exact test was applied if the theoretical frequency in the 2×2 table cell was less than 5. Cox regression analysis was used to analyse the relationship between clinicopathological characteristics, pretreatment HRR and OS. Kaplan–Meier curves with the log-rank test were used to evaluate the impact of hazard ratios (HRs) on OS. A Cox proportional hazards model with adjustment for pertinent variables was used to estimate the HR and 95% confidence intervals (CIs) for the risk of death associated with HRR. Each subgroup was defined according to the HRR cut-off value (dichotomous variable). The criterion for selecting the variable for adjustment was that if the change in HR after the variable was added to the model was >10% or the *P*-value in the univariate analysis was <0.05. The determined covariates were analysed in subgroups. A *P*-value <0.05 was considered statistically significant.

Results

A total of 808 patients were treated for NSCLC and 448 patients were eligible for inclusion in this analysis (Figure 1). The baseline clinicopathological characteristics of the pre-matching sample ($n = 448$) and the post-matching sample ($n = 284$) stratified based on the median HRR value of

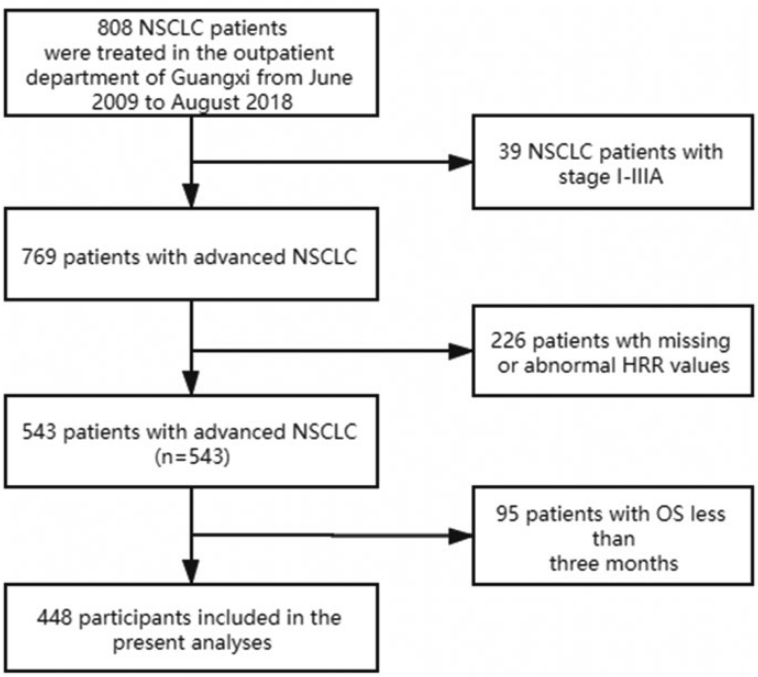

Figure 1. Flowchart of patient identification and enrolment based on the inclusion/exclusion criteria in this retrospective study to investigate the prognostic significance of haemoglobin-to-red cell distribution width ratio (HRR) in patients with non-small cell lung cancer (NSCLC).

0.984 are shown in Table 1. Overall, the mean ± SD age of the enrolled patients was 57.96 ± 11.05 years and 300 of 448 (66.96%) patients were male. When groups were compared before propensity matching, the group with HRR <0.984 were more likely to be female (39.01% versus 27.11%), non-smoking patients (52.02% versus 49.78%), have an ECOG PS of 2–4 (14.35% versus 8.44%), have a GPS of 1–2 (67.12% versus 37.05%), higher NLR (58.74% versus 43.56%) and higher PLR (58.74% versus 41.33%) compared with the group with HRR ≥0.984 ($P < 0.05$ for all comparisons). When the two groups were compared using the post-matching model, differences in all variables were reduced and had no significance.

The univariate analysis of the pre-matching ($n = 448$) and post-matching ($n = 284$) samples are shown in Table 2. The analysis using the pre-matching sample identified a positive relationship between HRR < 0.984 and the risk of death (HR 1.62, 95% CI 1.29, 2.02, $P < 0.0001$). The pre-matching analysis also showed significant associations between the risk of death and the following covariates: ever smoker (HR 1.26, 95% CI 1.00, 1.57, $P = 0.0466$), SCC (HR 1.39, 95% CI 1.07, 1.81, $P = 0.0152$) and GPS 1–2 (HR 1.41, 95% CI 1.13, 1.76, $P = 0.0026$). In addition, treatment with tyrosine kinase inhibitors (HR 0.64, 95% CI 0.44, 0.92, $P = 0.0166$) was predictive of a longer OS.

After using a PSM approach, HRR <0.984 (HR 1.55, 95% CI 1.17, 2.04, $P = 0.0021$) and ever smoker (HR 1.34, 95% CI 1.01, 1.77, $P = 0.0421$) remained significant predictors for the risk of death. Treatment with tyrosine kinase inhibitors (HR 0.60, 95% CI 0.37, 0.98, $P = 0.0420$) remained predictive of a longer OS. SCC and GPS 1–2 were no longer significant predictors in the post-matching model. The use of other treatment methods (HR 0.55, 95% CI 0.33, 0.93, $P = 0.0250$) was predictive of a longer OS.

The relationships between confounding covariates and OS in the pre-matching and post-matching samples are shown in Table 3. The Cox proportional hazard adjusted model analysis demonstrated that HRR < 0.984 was an independent predictive factor for OS both in the pre-matching model (HR 1.35, 95% CI 1.05, 1.74, $P = 0.0199$) and in the post-matching model (HR 1.57, 95% CI 1.17, 2.10, $P = 0.0027$).

Kaplan–Meier survival curve analysis before matching showed that the median survival of patients in the HRR <0.984 and HRR ≥0.984 groups was 11.17 months (95% CI 9.37, 13.30) and 18.77 months (95% CI 16.03, 23.00), respectively (Log-rank $P < 0.0001$) (Figure 2a). A similar finding was observed in post-matching groups: the median survival was 16.43 months (95% CI 13.40, 23.00) in the HRR ≥0.984 group compared with 11.2 months (95% CI 9.37, 14.50) in the HRR < 0.984 group (Log-rank $P = 0.0019$) (Figure 2b).

A subgroup analysis was undertaken to elucidate the effects of HRR on the risk of death after stratification by pertinent variables included in the present study. Before matching and after matching, the consistency of trends across all subsets of groups was in favour of HRR <0.984 compared with references, verifying the robustness of HRR as an independent factor in predicting survival in patients with advanced NSCLC.

Discussion

This current study demonstrated that a lower pretreatment HRR was related to a higher risk of death in patients with advanced NSCLC after a full set of covariates were adjusted for, suggesting that HRR could be a potentially valuable prognostic factor. To the best of our knowledge, this is the first study to use a PSM approach

Table 1. Baseline demographic and clinicopathological characteristics of patients with non-small cell lung cancer before and after propensity matching stratified according to the median haemoglobin-to-red cell distribution width ratio (HRR) value.

	Before propensity matching			After propensity matching		
Characteristic	HRR <0.984 $n=223$	HRR ≥0.984 $n=225$	Statistical significance[a]	HRR <0.984 $n=142$	HRR ≥0.984 $n=142$	Statistical significance[a]
Age, years			NS			NS
≤60	117 (52.47%)	138 (61.33%)		80 (56.34%)	76 (53.52%)	
>60	106 (47.53%)	87 (38.67%)		62 (43.66%)	66 (46.48%)	
Sex			$P=0.007$			NS
Female	87 (39.01%)	61 (27.11%)		46 (32.39%)	44 (30.99%)	
Male	136 (60.99%)	164 (72.89%)		96 (67.61%)	98 (69.01%)	
Smoking history			$P=0.006$			NS
Never	116 (52.02%)	112 (49.78%)		77 (54.23%)	72 (50.70%)	
Ever	98 (43.95%)	113 (50.22%)		60 (42.25%)	70 (49.30%)	
Unknown	9 (4.04%)	0 (0.00%)		5 (3.52%)	0 (0.00%)	
ECOG PS			$P=0.037$			NS
0–1	162 (72.65%)	186 (82.67%)		112 (78.87%)	112 (78.87%)	
2–4	32 (14.35%)	19 (8.44%)		14 (9.86%)	14 (9.86%)	
Unknown	29 (13.00%)	20 (8.89%)		16 (11.27%)	16 (11.27%)	
Pathology			NS			NS
ADC	155 (69.51%)	169 (75.11%)		107 (75.35%)	109 (76.76%)	
SCC	60 (26.91%)	43 (19.11%)		31 (21.83%)	25 (17.61%)	
Others	8 (3.59%)	13 (5.78%)		4 (2.82%)	8 (5.63%)	
GPS[b]			$P<0.001$			NS
0	73 (32.88%)	141 (62.95%)		64 (45.07%)	68 (47.89%)	
1–2	149 (67.12%)	83 (37.05%)		78 (54.93%)	74 (52.11%)	
NLR			$P=0.001$			NS
<3.3	92 (41.26%)	127 (56.44%)		66 (46.48%)	70 (49.30%)	
≥3.3	131 (58.74%)	98 (43.56%)		76 (53.52%)	72 (50.70%)	
PLR			$P<0.001$			NS
<176.32	92 (41.26%)	132 (58.67%)		70 (49.30%)	72 (50.70%)	
≥176.32	131 (58.74%)	93 (41.33%)		72 (50.70%)	70 (49.30%)	

(continued)

Table 1. Continued.

Characteristic	Before propensity matching			After propensity matching		
	HRR <0.984 $n = 223$	HRR ≥0.984 $n = 225$	Statistical significance[a]	HRR <0.984 $n = 142$	HRR ≥0.984 $n = 142$	Statistical significance[a]
EGFR mutation status			NS			NS
Positive	22 (9.87%)	39 (17.33%)		16 (11.27%)	18 (12.68%)	
Negative	51 (22.87%)	50 (22.22%)		36 (25.35%)	35 (24.65%)	
Unknown	150 (67.26%)	136 (60.44%)		90 (63.38%)	89 (62.68%)	
Sum of metastatic organs[b]			NS			NS
<2	107 (49.08%)	117 (53.42%)		74 (52.11%)	69 (48.59%)	
≥2	111 (50.92%)	102 (46.58%)		68 (47.89%)	73 (51.41%)	
Sum of treatment lines			NS			NS
First-line	109 (48.88%)	96 (42.67%)		57 (40.14%)	63 (44.37%)	
Second-line	32 (14.35%)	31 (13.78%)		24 (16.90%)	21 (14.79%)	
Third-line or more	36 (16.14%)	55 (24.44%)		31 (21.83%)	29 (20.42%)	
Unknown	46 (20.63%)	43 (19.11%)		30 (21.13%)	29 (20.42%)	
Treatment method			NS			NS
None	46 (20.63%)	43 (19.11%)		30 (21.13%)	29 (20.42%)	
Chemotherapy	115 (51.57%)	116 (51.56%)		71 (50.00%)	76 (53.52%)	
Tyrosine kinase inhibitors	37 (16.59%)	40 (17.78%)		23 (16.20%)	19 (13.38%)	
Other	25 (11.21%)	26 (11.56%)		18 (12.68%)	18 (12.68%)	

Data presented as *n* of patients (%).

[a]Categorical variables were analysed using Pearson's χ^2-test.

[b]Missing data for both groups before propensity matching.

ECOG PS, Eastern Cooperative Group performance status; ADC, adenocarcinoma; SCC, squamous cell carcinoma; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; EGFR, epidermal growth factor receptor; NS, no significant between-group difference ($P \geq 0.05$).

Table 2. Univariate analysis of the effect of variables on the risk of death in patients with non-small cell lung cancer before and after propensity matching.

	Before propensity matching			After propensity matching		
Variables	Statistics	HR (95% CI)	*P*-value	Statistics	HR (95% CI)	*P*-value
HRR						
≥0.984	225 (50.22%)	1.0		142(50.00%)	1.0	
<0.984	223 (49.78%)	1.62 (1.29, 2.02)	$P < 0.0001$	142 (50.00%)	1.55 (1.17, 2.04)	$P = 0.0021$
Age, years						
≤60	255 (56.92%)	1.0		156 (54.93%)	1.0	
>60	193 (43.08%)	1.11 (0.88, 1.38)	NS	128 (45.07%)	1.09 (0.83, 1.44)	NS
Sex						
Female	148 (33.04%)	1.0		90 (31.69%)	1.0	
Male	300 (66.96%)	1.13 (0.90, 1.43)	NS	194 (68.31%)	1.19 (0.89, 1.59)	NS
Smoking history						
Never	228 (50.89%)	1.0		149 (52.46%)	1.0	
Ever	211 (47.10%)	1.26 (1.00, 1.57)	0.0466	130 (45.77%)	1.34 (1.01, 1.77)	$P = 0.0421$
Unknown	9 (2.01%)	3.92 (1.98, 7.73)	$P < 0.0001$	5 (1.76%)	2.86 (1.16, 7.07)	$P = 0.0229$
ECOG PS						
0–1	348 (77.68%)	1.0		224 (78.87%)	1.0	
2–4	51 (11.38%)	1.31 (0.95, 1.82)	NS	28 (9.86%)	1.03 (0.65, 1.62)	NS
Unknown	49 (10.94%)	1.33 (0.96, 1.84)	NS	32 (11.27%)	1.25 (0.84, 1.87)	NS
Pathology						
ADC	324 (72.32%)	1.0		216 (76.06%)	1.0	
SCC	103 (22.99%)	1.39 (1.07, 1.81)	$P = 0.0152$	56 (19.72%)	1.29 (0.91, 1.84)	NS
Others	21 (4.69%)	1.10 (0.67, 1.84)	NS	12 (4.23%)	1.12 (0.59, 2.12)	NS
GPS[a]						
0	214 (47.98%)	1.0		132 (46.48%)	1.0	
1–2	232 (52.02%)	1.41 (1.13, 1.76)	$P = 0.0026$	152 (53.52%)	1.24 (0.94, 1.63)	NS
NLR						
<3.3	219 (48.88%)	1.0		136 (47.89%)	1.0	
≥3.3	229 (51.12%)	1.17 (0.94, 1.46)	NS	148 (52.11%)	1.07 (0.81, 1.41)	NS
PLR						
<176.32	224 (50.00%)	1.0		142 (50.00%)	1.0	

(continued)

Table 2. Continued.

Variables	Before propensity matching			After propensity matching		
	Statistics	HR (95% CI)	*P*-value	Statistics	HR (95% CI)	*P*-value
≥176.32	224 (50.00%)	1.09 (0.87, 1.36)	NS	142 (50.00%)	0.96 (0.73, 1.27)	NS
EGFR mutation status						
Positive	61 (13.62%)	1.0		34 (11.97%)	1.0	
Negative	101 (22.54%)	1.34 (0.89, 2.04)	NS	71 (25.00%)	1.27 (0.74, 2.17)	NS
Unknown	286 (63.84%)	1.47 (1.03, 2.10)	$P = 0.0348$	179 (63.03%)	1.30 (0.81, 2.07)	NS
Sum of metastatic organs[a]						
<2	224 (51.26%)	1.0		143 (50.35%)	1.0	
≥2	213 (48.74%)	1.12 (0.90, 1.41)	NS	141 (49.65%)	1.01 (0.77, 1.33)	NS
Sum of treatment lines						
First-line	205 (45.76%)	1.0		120 (42.25%)	1.0	
Second-line	63 (14.06%)	0.90 (0.65, 1.26)	NS	45 (15.85%)	1.01 (0.67, 1.50)	NS
Third-line or more	91 (20.31%)	0.65 (0.48, 0.89)	$P = 0.0067$	60 (21.13%)	0.69 (0.47, 1.01)	NS
Unknown	89 (19.87%)	1.17 (0.88, 1.57)	NS	59 (20.77%)	1.32 (0.92, 1.89)	NS
Treatment method						
None	89 (19.87%)	1.0		59 (20.77%)	1.0	
Chemotherapy	231 (51.56%)	0.81 (0.61, 1.08)	NS	147 (51.76%)	0.74 (0.52, 1.05)	NS
Tyrosine kinase inhibitors	77 (17.19%)	0.64 (0.44, 0.92)	$P = 0.0166$	42 (14.79%)	0.60 (0.37, 0.98)	$P = 0.0420$
Other	51 (11.38%)	0.65 (0.42, 1.00)	NS	36 (12.68%)	0.55 (0.33, 0.93)	$P = 0.0250$

Data presented as *n* of patients (%).

[a]Missing data for both groups before propensity matching.

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Group performance status; ADC, adenocarcinoma; SCC, squamous cell carcinoma; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; EGFR, epidermal growth factor receptor; NS, no significant between-group difference ($P \geq 0.05$).

Table 3. Cox proportional hazard analysis of the effect of haemoglobin-to-red cell distribution width ratio (HRR) value on overall survival in the entire and matched cohorts.

			Crude model		Adjusted model*	
Variable	*n*	Mortality	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Pre-matching						
HRR ≥0.984	225	147	1		1	
HRR <0.984	223	168	1.62 (1.29, 2.02)	$P < 0.0001$	1.35 (1.05, 1.74)	$P = 0.0199$
Post-matching						
HRR ≥0.984	142	95	1		1	
HRR <0.984	142	108	1.55 (1.17, 2.04)	$P = 0.0021$	1.57 (1.17, 2.10)	$P = 0.0027$

*The adjusted model adjusts for the following: age; sex; smoking history; Eastern Cooperative Group performance status; Glasgow prognostic score; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; pathology; epidermal growth factor receptor mutation; sum of metastatic organs; sum of treatment lines; and treatment method.
HR, hazard ratio; CI, 95% confidence interval.

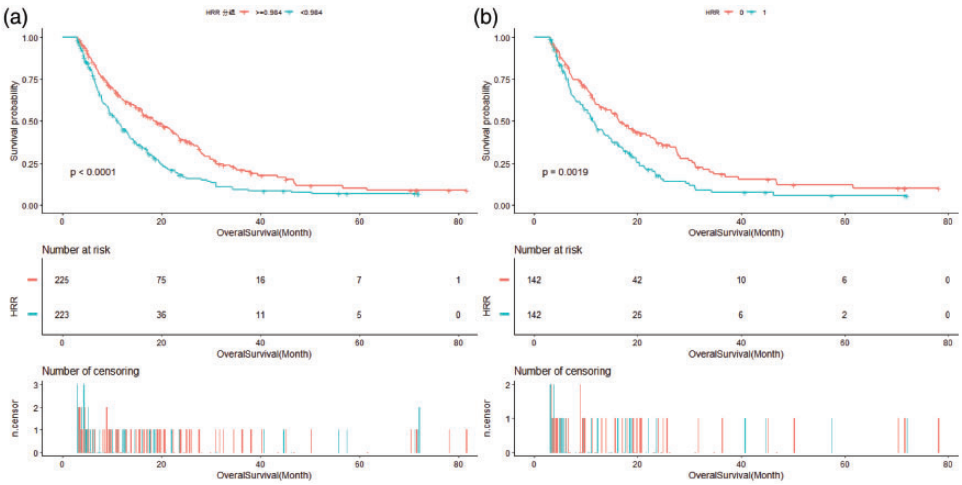

Figure 2. Kaplan–Meier curves before matching of overall survival stratified by haemoglobin-to-red cell distribution width ratio (HRR) <0.984 and HRR ≥0.984 groups (a) and after matching of overall survival stratified by HRR <0.984 and HRR ≥0.984 groups (b) in patients with non-small cell lung cancer. The colour version of this figure is available at: http://imr.sagepub.com.

to determine the predictive ability of HRR for overall survival in advanced NSCLC.

As one of the most common complications of various cancers, anaemia has been associated with shorter survival, especially in patients with advanced stage disease.[32,33] A poor prognosis was also observed in patients with NSCLC and lower baseline haemoglobin levels.[34,35] Multifactorial mechanisms may be involved in developing a disease caused by anaemia, such as activation of hypoxia-inducible factors, facilitating resistance to antitumour treatment, providing a more aggressive microenvironment and patients having a poor general function.[36–39]

Red cell distribution width is an index that reflects the size of red blood cells in

the peripheral blood circulation. The relationship between high RDW levels and increased risk of death in non-tumour system diseases has been well established and has gradually attracted attention in malignant tumours.[40–44] The RDW has recently been investigated as a prognostic marker for various cancer types, such as breast cancer, oesophageal cancer and gastric cancer.[45–47] A previous study reported a correlation between higher RDW values and lower survival in patients with lung cancer.[48] Given that both Hb and RDW are parameters that can reflect different aspects of red blood cell health, some researchers have attempted to integrate them into the HRR, with the aim of achieving a better and more reliable predictive biomarker than either Hb or RDW used alone. For example, several studies confirmed that HRR was superior to Hb and RDW in predicting the clinical outcome in neck and head cancer, gastric cancer, and oesophageal cancer.[22–24]

These current results were consistent with a previous study that analysed 153 patients with advanced NSCLC demonstrated that low HRR was associated with inferior OS (HR 1.607, 95% CI 1.041, 2.480, $P = 0.03$).[25] However, the cut-off value used by this previous study was a median HRR of 0.88, which was lower than the value used in the current study.[25] A study that included 245 patients with NSCLC, 97 patients with benign lung nodules and 94 healthy volunteers found that the HRR cut-off value was 9.48 determined through a receiver operating characteristic (ROC) curve analysis.[26] This was different to the selection of the HRR cut-off value in this current study. The cut-off value of 0.984 used in the present study was close to the first study that reported on the HRR.[24] In that retrospective analysis of a cohort of 362 Chinese patients with oesophageal cancer, an HRR of 0.989 was used as the cut-off value and a lower HRR (<0.989) was associated with shorter overall survival.[24] Since previous studies have used the median to determine the HRR cut-off value and a ROC curve analysis to determine the cut-off value,[25,26] there is no fixed standard for the HRR cut-off value. Therefore, in this current research, the median was selected as the HRR cut-off value. Whether the median HRR differs between different ethnicities or cancer types needs to be determined in further research. Another difference between the previous study of 153 patients with advanced NSCLC and this current research was that the epidermal growth factor receptor (EGFR) mutation status and treatment factors (e.g. sum of treatment lines) were used in the multivariate adjustment.[25] It is well established that these variables significantly impact the clinical outcomes, especially in the Asian race.[49,50]

Of note, this current study failed to show a longer overall survival in the EGFR mutation-positive subset of patients, which might be explained by the fact that the dataset ranged from a nearly 10-year period. As a consequence, some patients did not receive targeted therapy prior to their death. In addition, the small sample size of patients after stratification combined with an apparent discrepancy in OS resulted in a wide 95% confidence interval. Therefore, the relationship between EGFR mutation and overall survival in the present study should be treated with caution.

To eliminate any potential bias, this current study included the major variables that might influence the prognosis of advanced NSCLC and used the PSM approach to balance the characteristics between the low HRR and high HRR groups. Other variables such as GPS, NLR and PLR were also investigated. Neither GPS, NLR nor PLR were independently associated with OS. In contrast, a previous study reported that all of these variables could predict survival outcomes.[25]

This current study had two major strengths that differed from other similar studies.[25,26] First, a PSM approach was used to balance the characteristics of the low HRR and high HRR groups. Secondly, a subgroup analysis was undertaken to detect subset populations to verify the robustness of HRR as an independent index for predicting OS.

The present study had several limitations. First, it was a retrospective design and only included a limited number of patients from a single institute. Therefore, bias might have been hard to avoid. Secondly, the study only investigated the relationship between pretreatment HRR at diagnosis and OS. It remains to be determined whether any dynamic changes in HRR after treatment impact on OS. Thirdly, some parameters that might influence clinical outcomes (such as the Charlson comorbidity index) and HRR (such as intake of iron, ferritin, vitamin B12 and folic acid) could not be evaluated due to missing data.[51,52]

In conclusion, this current study demonstrated that lower pretreatment HRR might be a useful independent prognostic marker for OS in patients with advanced NSCLC. This preliminary finding should be further verified by prospective studies with larger cohorts.

Acknowledgements

The authors thank all of the staff members in our institutions.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the "139 Talent Planning" granted by Guangxi Health Commission, Guangxi Zhuang Autonomous Zone, China (no. 201903030).

ORCID iD

Shaozhang Zhou https://orcid.org/0000-0002-5471-4231

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; 144: 1941–1953.
2. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65: 5–29.
3. Moro-Sibilot D, Smit E, de Castro Carpeño J, et al. Outcomes and resource use of non-small cell lung cancer (NSCLC) patients treated with first-line platinum-based chemotherapy across Europe: FRAME prospective observational study. *Lung Cancer* 2015; 88: 215–222.
4. Zappa C and Mousa SA. Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res* 2016; 5: 288–300.
5. Zeng L, Xiao L, Jiang W, et al. Investigation of efficacy and acquired resistance for EGFR-TKI plus bevacizumab as first-line treatment in patients with EGFR sensitive mutant non-small cell lung cancer in a Real world population. *Lung Cancer* 2020; 141: 82–88.
6. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65: 5–29.
7. Zhu L, Chen S, Ma S, et al. Glasgow prognostic score predicts prognosis of non-small cell lung cancer: a meta-analysis. *Springerplus* 2016; 5: 439.
8. Jiang AG, Chen HL and Lu HY. The relationship between Glasgow Prognostic Score and serum tumor markers in patients with advanced non-small cell lung cancer. *BMC Cancer* 2015; 15: 386.
9. Grose D, Morrison DS, Devereux G, et al. The impact of comorbidity upon determinants of outcome in patients with lung cancer. *Lung Cancer* 2015; 87: 186–192.

10. Arslan D, Bozcuk H, Gunduz S, et al. Survival results and prognostic factors in T4 N0-3 non-small cell lung cancer patients according to the AJCC 7th edition staging system. *Asian Pac J Cancer Prev* 2014; 15: 2465–2472.
11. Zhou Y, Cui Z, Zhou X, et al. The presence of old pulmonary tuberculosis is an independent prognostic factor for squamous cell lung cancer survival. *J Cardiothorac Surg* 2013; 8: 123.
12. Pichler M, Hutterer GC, Stoeckigt C, et al. Validation of the pretreatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. *Br J Cancer* 2013; 108: 901–907.
13. Proctor MJ, Morrison DS, Talwar D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. *Eur J Cancer* 2011; 47: 2633–2641.
14. Yildirim M, Yildiz M, Duman E, et al. Prognostic importance of the nutritional status and systemic inflammatory response in non-small cell lung cancer. *J BUON* 2013; 18: 728–732.
15. Sugiura T, Uesaka K, Kanemoto H, et al. Elevated preoperative neutrophil-to-lymphocyte ratio as a predictor of survival after gastroenterostomy in patients with advanced pancreatic adenocarcinoma. *Ann Surg Oncol* 2013; 20: 4330–4337.
16. Gomez D, Farid S, Malik HZ, et al. Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. *World J Surg* 2008; 32: 1757–1762.
17. Dan J, Zhang Y, Peng Z, et al. Postoperative neutrophil-to-lymphocyte ratio change predicts survival of patients with small hepatocellular carcinoma undergoing radiofrequency ablation. *PLoS One* 2013; 8: e58184.
18. Lee S, Oh SY, Kim SH, et al. Prognostic significance of neutrophil-lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. *BMC Cancer* 2013; 13: 350.
19. Jankova L, Dent OF, Chan C, et al. Preoperative neutrophil/lymphocyte ratio predicts overall survival but does not predict recurrence or cancer-specific survival after curative resection of node-positive colorectal cancer. *BMC Cancer* 2013; 13: 442.
20. Cannon NA, Meyer J, Iyengar P, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. *J Thorac Oncol* 2015; 10: 280–285.
21. Wu F, Yang S, Tang X, et al. Prognostic value of baseline hemoglobin-to-red blood cell distribution width ratio in small cell lung cancer: A retrospective analysis. *Thorac Cancer* 2020; 11: 888–897.
22. Tham T, Olson C, Wotman M, et al. Evaluation of the prognostic utility of the hemoglobin-to-red cell distribution width ratio in head and neck cancer. *Eur Arch Otorhinolaryngol* 2018; 275: 2869–2878.
23. Yilmaz A, Mirili C, Tekin SB, et al. The ratio of hemoglobin to red cell distribution width predicts survival in patients with gastric cancer treated by neoadjuvant FLOT: a retrospective study. *Ir J Med Sci* 2020; 189: 91–102.
24. Sun P, Zhang F, Chen C, et al. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from southern China. *Oncotarget* 2016; 7: 42650–42660.
25. Bozkaya Y, Kurt B and Gurler F. A prognostic parameter in advanced non-small cell lung cancer: the ratio of hemoglobin-to-red cell distribution width. *Int J Clin Oncol* 2019; 24: 798–806.
26. Chen JL, Wu JN, Lv XD, et al. The value of red blood cell distribution width, neutrophil-to-lymphocyte ratio, and hemoglobin-to-red blood cell distribution width ratio in the progression of non-small cell lung cancer. *PLoS One* 2020; 15: e0237947.
27. Buccheri G, Ferrigno D and Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer* 1996; 32A: 1135–1141.
28. Teng XD. World Health Organization classification of tumours, pathology and

genetics of tumours of the lung. *Zhonghua Bing Li Xue Za Zhi* 2005; 34: 544–546 [Article in Chinese].
29. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007; 2: 706–714.
30. Lindenmann J, Fink-Neuboeck N, Taucher V, et al. Prediction of Postoperative Clinical Outcomes in Resected Stage I Non-Small Cell Lung Cancer Focusing on the Preoperative Glasgow Prognostic Score. *Cancers (Basel)* 2020; 12: 152.
31. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer* 2017; 111: 176–181.
32. Tesarova P and Kvasnicka J. Treatment of anemia in patients with tumors. *Cas Lek Cesk* 1995; 134: 647–650 [Article in Czech, English abstract].
33. Wilairat W and Benjapibal M. Presence of anemia and poor prognostic factors in patients with endometrial carcinoma. *Asian Pac J Cancer Prev* 2012; 13: 3187–3190.
34. Gauthier I, Ding K, Winton T, et al. Impact of hemoglobin levels on outcomes of adjuvant chemotherapy in resected non-small cell lung cancer: the JBR.10 trial experience. *Lung Cancer* 2007; 55: 357–363.
35. Zhang YH, Lu Y, Lu H, et al. Pretreatment Hemoglobin Level Is an Independent Prognostic Factor in Patients with Lung Adenocarcinoma. *Can Respir J* 2018; 2018: 6328127.
36. Banzet S, Sanchez H, Chapot R, et al. Interleukin-6 contributes to hepcidin mRNA increase in response to exercise. *Cytokine* 2012; 58: 158–161.
37. Wu Y, Antony S, Meitzler JL, et al. Molecular mechanisms underlying chronic inflammation-associated cancers. *Cancer Lett* 2014; 345: 164–173.
38. Graham K and Unger E. Overcoming tumor hypoxia as a barrier to radiotherapy, chemotherapy and immunotherapy in cancer treatment. *Int J Nanomedicine* 2018; 13: 6049–6058.
39. Kerins MJ and Ooi A. The Roles of NRF2 in Modulating Cellular Iron Homeostasis. *Antioxid Redox Signal* 2018; 29: 1756–1773.
40. Felker GM, Allen LA, Pocock SJ, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol* 2007; 50: 40–47.
41. Kim J, Kim YD, Song TJ, et al. Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. *Thromb Haemost* 2012; 108: 349–356.
42. Seyhan EC, Ozgul MA, Tutar N, et al. Red blood cell distribution and survival in patients with chronic obstructive pulmonary disease. *COPD* 2013; 10: 416–424.
43. Lou Y, Wang M and Mao W. Clinical usefulness of measuring red blood cell distribution width in patients with hepatitis B. *PLoS One* 2012; 7: e37644.
44. Podhorecka M, Halicka D, Szymczyk A, et al. Assessment of red blood cell distribution width as a prognostic marker in chronic lymphocytic leukemia. *Oncotarget* 2016; 7: 32846–32853.
45. Takeuchi H, Abe M, Takumi Y, et al. Elevated red cell distribution width to platelet count ratio predicts poor prognosis in patients with breast cancer. *Sci Rep* 2019; 9: 3033.
46. Han F, Liu Y, Cheng S, et al. Diagnosis and survival values of neutrophil-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) in esophageal cancer. *Clin Chim Acta* 2019; 488: 150–158.
47. Hirahara N, Tajima Y, Fujii Y, et al. Comprehensive Analysis of Red Blood Cell Distribution Width as a Preoperative Prognostic Predictor in Gastric Cancer. *Anticancer Res* 2019; 39: 3121–3130.
48. Koma Y, Onishi A, Matsuoka H, et al. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. *PLoS One* 2013; 8: e80240.

49. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014; 9: 154–162.
50. Mok TS, Cheng Y, Zhou X, et al. Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. *J Clin Oncol* 2018; 36: 2244–2250.
51. Zhao L, Leung LH, Wang J, et al. Association between Charlson comorbidity index score and outcome in patients with stage IIIB-IV non-small cell lung cancer. *BMC Pulm Med* 2017; 17: 112.
52. Hebuterne X, Lemarie E, Michallet M, et al. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN J Parenter Enteral Nutr* 2014; 38: 196–204.