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

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Abstract

Objective: To investigate the prognostic value of pretreatment haemoglobin-to-red cell distribution width ratio (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
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 ratio, overall survival, propensity score matching

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**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 non-smoker 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. The pathology was classified according to World Health Organization criteria (3rd version). The cancer staging was determined using the American Joint Committee on Cancer Guidelines (7th version). 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. NLR was calculated by division of the absolute neutrophil and lymphocyte counts. PLR was calculated by division of the absolute platelet and lymphocyte counts. 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 \( \chi^2 \)-test, respectively. Fisher’s exact test was applied if the theoretical frequency in the \( 2 \times 2 \) 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
| Characteristic          | Before propensity matching | After propensity matching | Statistical significance<sup>a</sup> | Before propensity matching | After propensity matching | Statistical significance<sup>a</sup> |
|------------------------|---------------------------|---------------------------|-------------------------------------|---------------------------|---------------------------|-------------------------------------|
|                        | HRR < 0.984 | HRR ≥ 0.984 |                        | HRR < 0.984 | HRR ≥ 0.984 |                        |
| n = 223                | n = 225       |                        | n = 142                 | n = 142       |                        |
| Age, years             |              |                        |                        |              |                        |                                    |
| ≤ 60                   | 117 (52.47%) | 138 (61.33%) | NS                     | 80 (56.34%)  | 76 (53.52%) | NS                    |
| > 60                   | 106 (47.53%) | 87 (38.67%)  |                        | 62 (43.66%)  | 66 (46.48%) |                        |
| Sex                    |              |                        |                        |              |                        |                                    |
| Female                 | 87 (39.01%)  | 61 (27.11%)  | P = 0.007               | 46 (32.39%)  | 44 (30.99%) | NS                    |
| Male                   | 136 (60.99%) | 164 (72.89%) |                        | 96 (67.61%)  | 98 (69.01%) | NS                    |
| Smoking history        |              |                        |                        |              |                        |                                    |
| Never                  | 116 (52.02%) | 112 (49.78%) | P = 0.006               | 77 (54.23%)  | 72 (50.70%) | NS                    |
| 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               |              |                        |                                    |
| 0–1                    | 162 (72.65%) | 186 (82.67%) |                        | 112 (78.87%) | 112 (78.87%) | NS                    |
| 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%) | NS                    |
| Pathology              |              |                        |                        |              |                        |                                    |
| ADC                    | 155 (69.51%) | 169 (75.11%) | NS                     | 107 (75.35%) | 109 (76.76%) | NS                    |
| 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<sup>b</sup>        |              |                        | P < 0.001               |              |                        |                                    |
| 0                      | 73 (32.88%)  | 141 (62.95%) |                        | 64 (45.07%)  | 68 (47.89%) | NS                    |
| 1–2                    | 149 (67.12%) | 83 (37.05%)  |                        | 78 (54.93%)  | 74 (52.11%) | NS                    |
| NLR                    |              |                        | P = 0.001               |              |                        |                                    |
| <3.3                   | 92 (41.26%)  | 127 (56.44%) |                        | 66 (46.48%)  | 70 (49.30%) | NS                    |
| ≥3.3                   | 131 (58.74%) | 98 (43.56%)  |                        | 76 (53.52%)  | 72 (50.70%) | NS                    |
| PLR                    |              |                        | P < 0.001               |              |                        |                                    |
| <176.32                | 92 (41.26%)  | 132 (58.67%) |                        | 70 (49.30%)  | 72 (50.70%) | NS                    |
| ≥176.32                | 131 (58.74%) | 93 (41.33%)  |                        | 72 (50.70%)  | 70 (49.30%) | NS                    |
Table 1. Continued.

| Characteristic                  | Before propensity matching | After propensity matching |
|---------------------------------|---------------------------|--------------------------|
|                                 | HRR < 0.984 | HRR ≥ 0.984 | Statistical significance\(^a\) | HRR < 0.984 | HRR ≥ 0.984 | Statistical significance\(^a\) |
| **Characteristic**              | n = 223     | n = 225     |                           | n = 142     | n = 142     |                           |
| 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 \(\chi^2\)-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.

| Variables          | Before propensity matching | After propensity matching |
|--------------------|----------------------------|---------------------------|
|                    | 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                 |            |             |         |            |             |         |
| 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 |
| \( \geq 176.32 \)            | 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         | NS | 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         | NS | 143 (50.35%) | 1.0         |       |
| \( \geq 2 \)                 | 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         | NS | 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         | NS | 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 (\( P \geq 0.05 \)).
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.\textsuperscript{32,33} A poor prognosis was also observed in patients with NSCLC and lower baseline haemoglobin levels.\textsuperscript{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.\textsuperscript{36–39}

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

### 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.

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

*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.
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. The RDW has recently been investigated as a prognostic marker for various cancer types, such as breast cancer, oesophageal cancer and gastric cancer. A previous study reported a correlation between higher RDW values and lower survival in patients with lung cancer. 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.

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, \( P = 0.03 \)). 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. 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. 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. 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. 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, 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. It is well established that these variables significantly impact the clinical outcomes, especially in the Asian race.

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.
This current study had two major strengths that differed from other similar studies. 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.

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.

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