Original Article

Preoperative hemoglobin-to-red cell distribution width ratio as a prognostic factor in pulmonary large cell neuroendocrine carcinoma: a retrospective cohort study

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Background: The hemoglobin (Hgb)/red cell distribution width (RDW) ratio (HRR) is a simple prognostic marker for small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), but no data are available for pulmonary large cell neuroendocrine carcinoma (PLCNEC). This study aimed to assess the potential prognostic role of preoperative HRR in PLCNEC.

Methods: This single-center retrospective study included patients with PLCNEC who underwent surgery at Shanghai Pulmonary Hospital from January 2012 to August 2016. The follow-up was censored in August 2020. The participants were grouped as low/high HRR according to their optimal value calculated using a receiver operating characteristic (ROC) curve. Univariable and multivariable Cox analysis were performed to identify the risk factors for overall survival (OS).

Results: A total of 80 patients with PLCNEC were included. The optimal cutoff values were 0.969 for HRR. Compared with the high HRR group, the low HRR group had a lower mean Hgb (12.1 *vs.* 14.1 g/dL, P<0.001), lower mean albumin-globulin ratio (AGR) (1.4 *vs.* 1.6, P=0.017), and higher median RDW (14.5% *vs.* 12.9%, P<0.001). The median OS was 30.0 months [95% confidence interval (CI): 13.4 to 46.5 months]. Participants in the low HRR group exhibited a poorer OS than those with high HRR (20.3 months, 95% CI: 14.5 to 26.1 months *vs.* not reached, P<0.001). The multivariable analysis showed that low HRR was significantly associated with poor OS [hazard ratio (HR) =3.16, 95% CI: 1.69 to 5.93, P<0.001].

Conclusions: Low HRR is associated with poor OS in patients with PLCNEC and can be used as an inexpensive prognostic factor in patients undergoing PLCNEC resection.

Keywords: Pulmonary large cell neuroendocrine carcinoma (PLCNEC); hemoglobin (Hgb); red blood cell distribution ratio; hemoglobin-to-red blood cell distribution ratio (HRR); overall survival (OS)

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Introduction

Pulmonary large cell neuroendocrine carcinoma (PLCNEC) is a rare malignant carcinoma, accounting for 2.1–3.5% of lung cancers (1-3). Like small cell lung cancer (SCLC), PLCNEC has an aggressive behavior and poor prognosis (1-4). An analysis of the Surveillance, Epidemiology, and End Results (SEER) database showed that the 3-year overall survival (OS) and 5-year OS rates of PLCNEC were 22.8% and 16.8%, respectively (5). The survival is poor even for patients undergoing surgery, with a reported

5-year OS of approximately 10–30% (6-8). Because of the low prevalence rate, there were only few retrospective studies (9-11) investigated the prognosis factor for OS in PLCNEC after surgery. PLCNEC patients with elder age, advanced stage and nodal involvement, bilobectomy or pneumonectomy resection, and coexpression of more than one neuroendocrine marker have poor prognosis. Therefore, finding effective prognostic indicators is relevant to guide treatments.

Studies have shown that nutritional status is closely related to tumor prognosis (12,13). Nutritional risk is one of the most predictive and treatable components of oncologic assessment (14). Low hemoglobin (Hgb) levels reflect malnutrition and the host's immune status, and anemia predicts poor cancer outcomes (15-17). The red cell distribution width (RDW) is a measure of the variability of the size of the red cells. Elevated RDW reflects a deregulation of erythrocyte homeostasis, which may be attributed to a variety of underlying metabolic abnormalities. The RDW is mainly used for the differential diagnosis of anemia. Emerging evidence suggests that RDW is correlated with advanced cancer stage in non-small cell lung cancer (NSCLC) (18,19) and is a prognostic marker of cancer (20-22).

Nevertheless, the 2 parameters might be affected by diseases other than tumors (23). In order to minimize this influence, Hgb/RDW ratio (HRR) was found to be a more reliable parameter for survival prognosis in various solid tumors. The HRR is a simple prognostic marker first proposed in 2016 for esophageal cancer (24), and has been shown to also have prognostic value for cancer of gastric (25), bladder (26), renal (27), head and neck (28), SCLC (29) and NSCLC (30). Those studies suggested that a low HRR is associated with poor prognosis. To date, no data are available regarding the prognostic value of the HRR in PLCNEC.

Therefore, this study aimed to assess the potential prognostic role of HRR in PLCNEC. The results could provide a simple and easily obtained marker for the prognosis of PLCNEC and management individualization. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6348/rc).

Methods

Study design and patients

This single-center retrospective study included patients with PLCNEC who underwent surgery at Shanghai Pulmonary Hospital from January 2012 to August 2016. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Research Ethics Committee of Shanghai Pulmonary Hospital (No. K18-034-1). Individual consent for this retrospective analysis was waived. The inclusion criteria were as follows: (I) patients underwent complete resection (R0); (II) PLCNEC diagnosed by immunohistochemistry (IHC) according to the WHO criteria; (III) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1; and (IV) complete blood test data available within 1 week before surgery. The exclusion criteria were as follows: (I) second concomitant primary tumor; (II) hematological disease; (III) Hgb <9 g/dL; or (IV) survival of <2 months after surgery.

Data collection

Clinical data, including gender, age, smoking history, ECOG PS, and body mass index (BMI) before surgery were collected from electronic medical records. The operation type, pathologic tumor-node-metastasis (TNM) stage (seventh edition), and systemic treatments were recorded in electronic medical records. Laboratory hematological parameters such as Hgb (g/dL), RDW (%), and albumin-globulin ratio (AGR) were measured within 1 week before the operation. The HRR was calculated from the following formula: Hgb (g/dL) divided by RDW (%).

Follow-up

The follow-up data were taken from the medical charts from January 2012 to August 2020. The patients were routinely followed through outpatient visits or phone calls. The OS was determined as the time from surgery to death.

Statistical analysis

Data analysis was performed using the software SPSS 26.0 (IBM Corp., Chicago, IL, USA). The patients were divided into low and high HRR groups. The optimal cutoff value was determined using the area under the receiver operating characteristic (ROC) curve (AUC), calculated by a time-dependent survival ROC curve package (survival ROC) in R language (version 3.6.3; https://cran.r-project.org/bin/windows/base/old/3.6.3/). Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Those with a normal distribution were presented as mean ±

standard deviation and were analyzed using Student's *t*-test; otherwise, they were presented as median [interquartile range (IQR)] and tested using the Mann-Whitney U-test. Categorical data were presented as n (%) and tested using the chi-square test. The OS was analyzed by the Kaplan-Meier method and the log-rank test. Univariable and multivariable Cox regression models were used to determine the independent prognosis factors for OS. All statistical tests were bilateral, and P values <0.05 were considered statistically significant.

Results

Characteristics of the patients

A total of 80 patients were included in this study. The clinical characteristics are shown in *Table 1*. The median age at admission was 66 (IQR, 40–83) years, 88.8% (71/80) of the patients were male, and 53.8% (43/80) had a history of smoking. The mean BMI was 23.1 (IQR, 17.0–31.2) kg/m^2. All participants had an ECOG PS of 0 or 1. Among all participants, 71.3% of patients underwent lobectomy, 20.0% underwent segmentectomy, and 8.8% underwent pneumonectomy. The mean Hgb levels were 13.3 (IQR, 9.3–16.9) g/dL. The median RDW was 13.2% (IQR, 11.8–17.8%). The mean AGR was 1.5 (IQR, 0.9–2.2). The time-dependent survival ROC curve determined that the optimal cutoff values were 0.969 for HRR, 13.0 g/dL for Hgb, 14.2% for RDW, 1.4 for AGR, and 24.2 kg/m^2 for BMI.

Relationship between HRR and clinicopathological characteristics

The participants were divided according to the optimal cutoff value of HRR of 0.969. As shown in *Table 1*, compared with the high HRR group, the low HRR group had lower mean Hgb (12.1 *vs.* 14.1 g/dL, P<0.001), lower mean AGR (1.4 *vs.* 1.6, P=0.017), and higher median RDW (14.5% *vs.* 12.9%, P<0.001).

OS

The median follow-up was 65.8 (IQR, 2.7–93.7) months, and 61.3% (49/80) patients died during follow-up. The 1-, 3-, and 5-year OS rates were 69%, 44%, and 39%, respectively. The median OS was 30.0 months (95% CI: 13.4 to 46.5 months) in the entire cohort (*Figure 1*). The patients in the low HRR group showed a significantly poorer OS than those with high HRR [20.3 months, 95% CI: 14.5 to 26.1 months *vs.* not reached (NR), P<0.001] (*Figure 2*).

Univariable and multivariable analysis

In the univariable Cox proportional hazard regression analysis for OS, gender (P=0.019), TNM stage (P=0.037), surgical mode (P=0.048), and HRR (P<0.001) were significantly associated with OS. Although not significant, ECOG PS and BMI tended towards statistical significance (P=0.090 and P=0.094, respectively). All these variables were included in the multivariable analysis. The results showed that low HRR (HR =3.16, 95% CI: 1.69 to 5.93, P<0.001), early TNM stage (HR =0.53, 95% CI: 0.29 to 0.96, P=0.037), and low ECOG PS (HR =0.48, 95% CI: 0.24 to 0.92, P=0.028) were independently associated with OS (*Table 2*).

Discussion

The HRR is a simple prognostic marker for SCLC and NSCLC, but no data are available for PLCNEC. This study aimed to assess the potential prognostic role of preoperative HRR in PLCNEC. The results suggested that low HRR is associated with poor OS in patients with PLCNEC. The HRR could be used as an inexpensive and easily available prognostic factor in patients undergoing PLCNEC resection.

Anemia is very common in cancer patients, with an incidence of about 30% (31). Gauthier *et al.* (32) showed a poor prognosis in NSCLC patients with low baseline Hgb levels (<12 g/dL). In SCLC patients, anemia (Hgb <13 g/dL in males and <12 g/dL in females) at SCLC diagnosis was an independent prognostic marker of OS (33). For stage I NSCLC patients treated with stereotactic body radiation therapy (SBRT), anemia at baseline is associated with increased local and distant recurrence rates and poorer OS (34). A meta-analysis (35) including 10,612 lung cancer patients showed that, pre-operative anemia was a negative prognostic factor (summarized HR =1.58, 95% CI: 1.44 to 1.75). To the best of our knowledge, there is currently no available data specific to PLCNEC patients. Still, the mechanism of the association between anemia and poor OS is not clear. Possible explanations are that (I) more severe anemia represents a higher degree and invasiveness of the tumor, (II) hypoxic conditions due to anemia can induce the tumor to transform into a more invasive phenotype and

Table 1 Baseline clinical features of 80 patients with PLCNEC

Characteristics	Total (n=80)	Low HRR (n=29)	High HRR (n=51)	P value
Age, years, median [IQR]	66 [40–83]	66 [46–83]	65 [40–77]	
≤65, n (%)	38 (47.5)	12 (41.4)	26 (51.0)	0.408
>65, n (%)	42 (52.5)	17 (58.6)	25 (49.0)	
Gender, n (%)				0.065
Female	9 (11.3)	6 (20.7)	3 (5.9)	
Male	71 (88.8)	23 (79.3)	48 (94.1)	
Smoking history, n (%)				0.847
Ever	43 (53.8)	16 (55.2)	27 (52.9)	
Never	37 (46.3)	13 (44.8)	24 (47.1)	
ECOG PS, n (%)				0.699
0	27 (33.8)	9 (31.0)	18 (35.3)	
1	53 (66.3)	20 (69.0)	33 (64.7)	
T stage, n (%)				0.963[a]
T1	33 (41.3)	12 (41.4)	21 (41.2)	
T2	33 (41.3)	12 (41.4)	21 (41.2)	
T3	10 (12.5)	4 (13.8)	6 (11.8)	
T4	4 (5.0)	1 (3.4)	3 (5.9)	
N stage, n (%)				0.624[b]
N0	47 (58.8)	16 (55.2)	31 (60.8)	
N1	9 (11.3)	3 (10.3)	6 (11.8)	
N2	22 (27.5)	9 (31.0)	13 (25.5)	
N3	2 (2.5)	1 (3.4)	1 (2.0)	
TNM stage, n (%)				0.638[c]
I	36 (45.0)	12 (41.4)	24 (47.1)	
II	19 (23.8)	7 (24.1)	12 (23.5)	
III	25 (31.3)	10 (34.5)	15 (29.4)	
Resection mode, n (%)				0.862[d]
Lobectomy	57 (71.3)	21 (72.4)	36 (70.6)	
Segmentectomy	16 (20.0)	5 (17.2)	11 (21.6)	
Pneumonectomy	7 (8.8)	3 (10.3)	4 (7.8)	
BMI, kg/m^2, mean ± SD	23.1±3.0	22.8±3.5	23.3±2.7	0.457
Hgb, g/dL, mean ± SD	13.3±15.0	12.1±11.4	14.1±12.0	<0.001
RDW, %, median (IQR)	13.2 (1.4)	14.5 (1.5)	12.9 (0.7)	<0.001
AGR, mean ± SD	1.5±0.3	1.4±0.3	1.6±0.3	0.017

P values <0.05 were considered statistically significant. [a], TI + T2 *vs.* T3 + T4; [b], N0 *vs.* N1 + N2 +N3; [c], stage I + II *vs*. stage III; [d], lobectomy *vs.* segmentectomy + pneumonectomy. PLCNEC, pulmonary large cell neuroendocrine carcinoma; SD, standard deviation; IQR, interquartile range; ECOG PS, Eastern Corporation Oncology Group Performance Status; BMI, body mass index; TNM stage, tumor-node-metastasis stage; Hgb, hemoglobin; RDW, red blood cell distribution width; HRR, hemoglobin/red blood cell distribution width ratio; AGR, albumin-globulin ratio.

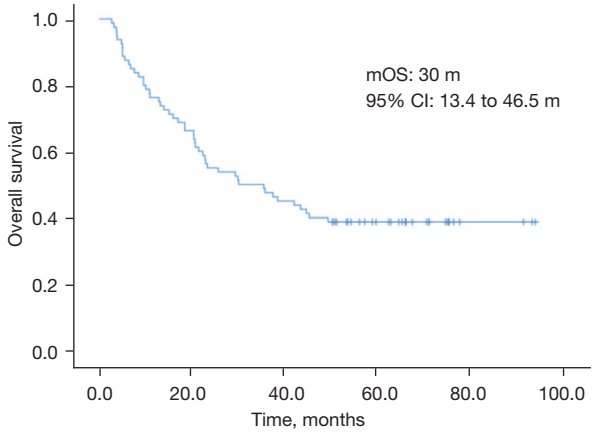

Figure 1 Kaplan-Meier curves for OS. OS, overall survival; mOS, median overall survival.

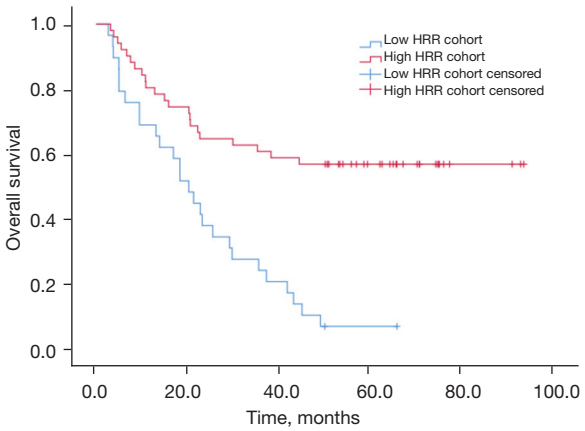

Figure 2 Kaplan-Meier curves for OS according to the HRR. OS, overall survival; HRR, hemoglobin-to-red blood cell distribution ratio.

Table 2 Univariable and multivariable Cox analysis of overall survival

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years): ≤65 *vs.* >65	1.08 (0.62–1.89)	0.796		
Gender: male *vs.* female	0.41 (0.20–0.86)	0.019	0.62 (0.27–1.40)	0.247
Smoking: never *vs.* ever	0.82 (0.47–1.44)	0.482		
ECOG PS: 0 *vs.* 1	0.58 (0.31–1.09)	0.090	0.48 (0.24–0.92)	0.028
BMI (kg/m^2): <24.2 *vs.* ≥24.2	1.68 (0.92–3.10)	0.094	1.39 (0.73–2.63)	0.313
T stage: T1–2 *vs.* T3–4	0.56 (0.28–1.12)	0.102		
N stage: N0 *vs.* N1–3	0.59 (0.34–1.04)	0.068		
TNM stage: I–II *vs.* III	0.54 (0.30–0.96)	0.037	0.53 (0.29–0.96)	0.037
Lobectomy *vs.* non- lobectomy	0.55 (0.31–1.00)	0.048	0.65 (0.35–1.19)	0.159
Neoadjuvant chemotherapy: yes *vs.* no	1.20 (0.43–3.33)	0.732		
Adjuvant chemotherapy: yes *vs.* no	0.72 (0.41–1.26)	0.245		
Hgb (g/dL): <13.0 *vs.* ≥13.0	2.88 (1.62–5.10)	<0.001		
RDW (%): <14.2 *vs.* ≥14.2	0.40 (0.22–0.72)	0.002		
HRR: <0.969 *vs.* ≥0.969	3.28 (1.85–5.83)	<0.001	3.16 (1.69–5.93)	<0.001
AGR: <1.4 *vs.* ≥1.4	1.34 (0.71–2.53)	0.368		

P values <0.05 were considered statistically significant. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Corporation Oncology Group Performance Status; BMI, body mass index; TNM stage, tumor-node-metastasis stage; Hgb, hemoglobin; RDW, red blood cell distribution width; HRR, hemoglobin/red blood cell distribution width ratio; AGR, albumin-globulin ratio.

decrease the sensitivity to chemotherapy or radiotherapy, and (III) anemia can lead to the release of some cytokines such as tumor necrosis factor-α and interleukin-6 (36-40). Additional studies are necessary to determine the link between anemia and cancer progression. Nutritional status and poor physical resistance could be involved in this poor prognosis (12,13,41,42).

The RDW is a marker used in the diagnosis of anemia. Koma *et al.* (19) and Warwick *et al.* (18) reported that high RDW (values of ≥15%) was associated with poor prognosis in NSCLC. Similarly, Wu *et al.* (29) reported that high RDW (>13.6%) was an independent risk factor of progression-free survival (PFS) in SCLC patients. In a study of patients who underwent NSCLC resection, high RDW was significantly associated with higher morbidity (43).

Although the Hgb and RDW have been shown to have prognostic value in lung cancer patients, the 2 parameters might be affected by diseases other than tumors. In order to minimize this influence, HRR was found to be a more reliable parameter for survival prognosis in various solid tumors. Indeed, Sun *et al.* (24) reported that low HRR (<0.989) was a prognostic risk factor of OS in esophageal cancer, but not Hgb or RDW. Tham *et al.* (44) showed that HRR was a predictor of event-free survival (EFS) in head and neck cancers. Bozkaya *et al.* (45) showed similar results that low HRR (<0.88) was associated with poor OS and PFS in patients with NSCLC. The results of the study conducted in SCLC are also consistent (29). To the best of the authors' knowledge, the present study is the first to report the association between HRR and survival in PLCNEC. In this study, the multivariable analysis of OS showed that low-level HRR (<0.969) was an independent prognostic factor in PLCNEC (HR =3.16, 95% CI: 1.69 to 5.93) along with ECOG PS and TNM stage, while all other parameters were not significant. In addition to HRR, AGR and BMI are often used to assess nutritional status. In this study, BMI showed a tendency towards predictive value in the univariable analysis but not in the multivariable analysis, which might be related to the small sample size.

This study has some limitations. First, since this was a retrospective study, it was impossible to rule out any potential factors affecting the outcomes, such as autoimmune or inflammatory diseases. Second, the sample size was too small and might have led to bias.

In conclusion, this study was the first to investigate the prognostic value of HRR in PLCNEC patients. The multivariable predictive model suggested that HRR is an independent predictor of OS. The HRR can be used as an easily available and inexpensive prognostic factor in patients undergoing PLCNEC resection. Future prospective and large-sample studies are needed to confirm the prognostic value of HRR.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6348/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6348/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6348/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Research Ethics Committee of Shanghai Pulmonary Hospital (No. K18-034-1). Individual consent for this retrospective analysis was waived.

References

1. Fasano M, Della Corte CM, Papaccio F, et al. Pulmonary Large-Cell Neuroendocrine Carcinoma: From Epidemiology to Therapy. J Thorac Oncol 2015;10:1133-41.
2. Hiroshima K, Mino-Kenudson M. Update on large cell neuroendocrine carcinoma. Transl Lung Cancer Res 2017;6:530-9.
3. Yang Q, Xu Z, Chen X, et al. Clinicopathological characteristics and prognostic factors of pulmonary large cell neuroendocrine carcinoma: A large population-based analysis. Thorac Cancer 2019;10:751-60.
4. Eichhorn F, Dienemann H, Muley T, et al. Predictors of survival after operation among patients with large cell neuroendocrine carcinoma of the lung. Ann Thorac Surg 2015;99:983-9.
5. Tsoukalas N, Baxevanos P, Aravantinou-Fatorou E, et al. Advances on systemic treatment for lung neuroendocrine neoplasms. Ann Transl Med 2018;6:146.
6. Fernandez FG, Battafarano RJ. Large-cell neuroendocrine carcinoma of the lung: an aggressive neuroendocrine lung cancer. Semin Thorac Cardiovasc Surg 2006;18:206-10.
7. Sánchez de Cos Escuín J. Diagnosis and treatment of neuroendocrine lung tumors. Arch Bronconeumol 2014;50:392-6.
8. Battafarano RJ, Fernandez FG, Ritter J, et al. Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. J Thorac Cardiovasc Surg 2005;130:166-72.
9. Veronesi G, Morandi U, Alloisio M, et al. Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. Lung Cancer 2006;53:111-5.
10. Roesel C, Terjung S, Weinreich G, et al. A Single-Institution Analysis of the Surgical Management of Pulmonary Large Cell Neuroendocrine Carcinomas. Ann Thorac Surg 2016;101:1909-14.
11. Girelli L, Casiraghi M, Sandri A, et al. Results of Surgical Resection of Locally Advanced Pulmonary Neuroendocrine Tumors. Ann Thorac Surg 2021;112:405-14.
12. Mantzorou M, Koutelidakis A, Theocharis S, et al. Clinical Value of Nutritional Status in Cancer: What is its Impact and how it Affects Disease Progression and Prognosis? Nutr Cancer 2017;69:1151-76.
13. Torbahn G, Strauss T, Sieber CC, et al. Nutritional status according to the mini nutritional assessment (MNA)® as potential prognostic factor for health and treatment outcomes in patients with cancer - a systematic review. BMC Cancer 2020;20:594.
14. Huisman MG, Kok M, de Bock GH, et al. Delivering tailored surgery to older cancer patients: Preoperative geriatric assessment domains and screening tools - A systematic review of systematic reviews. Eur J Surg Oncol 2017;43:1-14.
15. Ye X, Liu J, Chen Y, et al. The impact of hemoglobin level and transfusion on the outcomes of chemotherapy in gastric cancer patients. Int J Clin Exp Med 2015;8:4228-35.
16. Shin NR, Lee YY, Kim SH, et al. Prognostic value of pretreatment hemoglobin level in patients with early cervical cancer. Obstet Gynecol Sci 2014;57:28-36.
17. Guo SS, Tang LQ, Chen QY, et al. Is Hemoglobin Level in Patients with Nasopharyngeal Carcinoma Still a Significant Prognostic Factor in the Era of Intensity-Modulated Radiotherapy Technology? PLoS One 2015;10:e0136033.
18. Warwick R, Mediratta N, Shackcloth M, et al. Preoperative red cell distribution width in patients undergoing pulmonary resections for non-small-cell lung cancer. Eur J Cardiothorac Surg 2014;45:108-13.
19. 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.
20. Ellingsen TS, Lappegård J, Skjelbakken T, et al. Impact of red cell distribution width on future risk of cancer and all-cause mortality among cancer patients - the Tromsø Study. Haematologica 2015;100:e387-9.
21. Seretis C, Seretis F, Lagoudianakis E, et al. Is red cell distribution width a novel biomarker of breast cancer activity? Data from a pilot study. J Clin Med Res 2013;5:121-6.
22. Wang FM, Xu G, Zhang Y, et al. Red cell distribution width is associated with presence, stage, and grade in patients with renal cell carcinoma. Dis Markers 2014;2014:860419.
23. Hammons L, Filopei J, Steiger D, et al. A narrative review of red blood cell distribution width as a marker for pulmonary embolism. J Thromb Thrombolysis 2019;48:638-47.
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;7:42650-60.
25. Yılmaz 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.
26. Yılmaz A, Yılmaz H, Tekin SB, et al. The prognostic significance of hemoglobin-to-red cell distribution width ratio in muscle-invasive bladder cancer. Biomark Med 2020;14:727-38.
27. Yılmaz H, Yılmaz A, Demirağ G. Prognostic significance of hemoglobin-to-red cell distribution width ratio in patients with metastatic renal cancer. Future Oncol 2021;17:3853-64.
28. Melo-Alvim C, Miguel-Semedo P, Paiva RS, et al. Pretreatment hemoglobin level as a prognostic factor in patients with locally advanced head and neck squamous cell carcinoma. Rep Pract Oncol Radiother 2020;25:768-74.
29. 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;11:888-97.
30. 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.
31. Katodritou E, Dimopoulos MA, Zervas K, et al. Update on the use of erythropoiesis-stimulating agents (ESAs) for the management of anemia of multiple myeloma and lymphoma. Cancer Treat Rev 2009;35:738-43.
32. 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;55:357-63.
33. Aoe K, Hiraki A, Maeda T, et al. Serum hemoglobin level determined at the first presentation is a poor prognostic indicator in patients with lung cancer. Intern Med 2005;44:800-4.
34. Pathak RS, Pantarotto JR, Cook G, et al. Anemia is a poor prognostic factor for stage I non-small cell lung cancer (NSCLC) patients treated with Stereotactic Body Radiation Therapy (SBRT). Clin Transl Radiat Oncol 2019;16:28-33.
35. Liu Y, Bai YP, Zhou ZF, et al. Preoperative anemia as a prognostic factor in patients with lung cancer: a systematic review and meta-analysis of epidemiological studies. J Cancer 2019;10:2047-56.
36. Li S, Meng W, Guan Z, et al. The hypoxia-related signaling pathways of vasculogenic mimicry in tumor treatment. Biomed Pharmacother 2016;80:127-35.
37. Wu Y, Antony S, Meitzler JL, et al. Molecular mechanisms underlying chronic inflammation-associated cancers. Cancer Lett 2014;345:164-73.
38. Banzet S, Sanchez H, Chapot R, et al. Interleukin-6 contributes to hepcidin mRNA increase in response to exercise. Cytokine 2012;58:158-61.
39. Lewis C, Murdoch C. Macrophage responses to hypoxia: implications for tumor progression and anti-cancer therapies. Am J Pathol 2005;167:627-35.
40. Schito L, Semenza GL. Hypoxia-Inducible Factors: Master Regulators of Cancer Progression. Trends Cancer 2016;2:758-70.
41. Joffe L, Dwyer S, Glade Bender JL, et al. Nutritional status and clinical outcomes in pediatric patients with solid tumors : A systematic review of the literature. Semin Oncol 2019;46:48-56.
42. Bullock AF, Greenley SL, McKenzie GAG, et al. Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis and meta-analysis. Eur J Clin Nutr 2020;74:1519-35.
43. Ichinose J, Murakawa T, Kawashima M, et al. Prognostic significance of red cell distribution width in elderly patients undergoing resection for non-small cell lung cancer. J Thorac Dis 2016;8:3658-66.
44. 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;275:2869-78.
45. Bozkaya Y, Kurt B, Gürler 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.

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