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

Wencheng Zhao[#], Minxing Shi[#], Jie Zhang

Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: J Zhang; (II) Administrative support: J Zhang; (III) Provision of study materials or patients: J Zhang; (IV) Collection and assembly of data: M Shi, W Zhao; (V) Data analysis and interpretation: W Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jie Zhang. Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, 507 Zhengmin Road, Yangpu District, Shanghai 200433, China. Email: zhangjie2172@163.com.

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)

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

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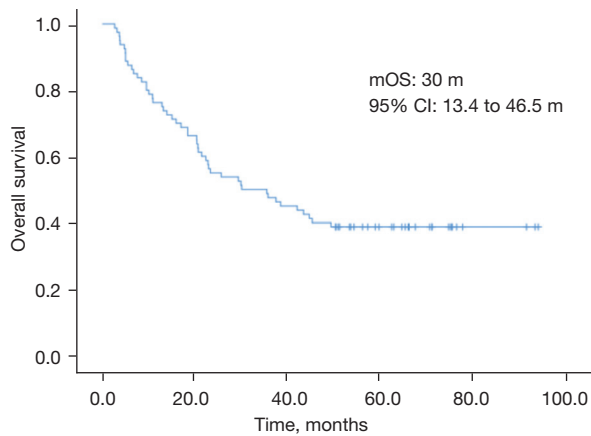
Figure 1 Kaplan-Meier curves for OS. OS, overall survival; mOS, median overall survival.
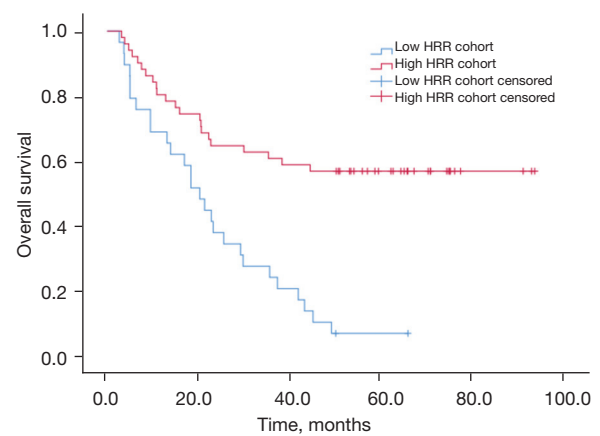

Figure 2 Kaplan-Meier curves for OS according to the HRR. OS, overall survival; HRR, hemoglobin-to-red blood cell distribution ratio.

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/m²): <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.

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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.

Acknowledgments

Footnote

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