European Review for Medical and Pharmacological Sciences 2023; 27: 2060-2067

The relationship between hemoglobin-RDW ratio and clinical outcomes in patients with advanced pancreas cancer

A. İLHAN, F. GURLER, F. YILMAZ, E. ERASLAN, M. DOGAN

Department of Medical Oncology, University of Health Sciences Ankara, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: The prognostic significance of hemoglobin (HGB) -red cell distribution width (RDW) ratio (HRR) has been indicated in various cancer types. However, its clinical significance in patients with metastatic pancreas cancer (MPC) is unknown. In this study, we aimed to investigate the prognostic importance of pre-treatment HRR in patients with metastatic pancreas cancer.

PATIENTS AND METHODS: MPC patients (≥18 years of age) who received at least one course of chemotherapy between January 2001 and January 2021, were evaluated retrospectively in terms of pre-treatment HRR values.

RESULTS: Of 111 patients, the mean HRR value was 0.84, and the patients were divided into low HRR and high HRR groups. The median follow-up was 8.7 months (95% CI 1.8-51.6). The median duration of first-line treatment was 4.4 months (95% CI 0.5-31.3). The median overall survival (OS) was 7.6 months (95% CI 3.4-11.8) in the low HRR group and 8.7 months (95% CI 5.7-11.8 months) in the high HRR group (p=0.276) (Figure 1). The median progression-free survival (PFS) was 4.2 months (95% CI 2.7-5.6 months) in the low HRR group and 5.1 months (95% CI 2.8-7.4 months) in the high HRR group (p=0.044) It was found that high HRR decreased progression event in both univariate (HR 0.67, 95% CI 0.45-0.99, p=0.046) and multivariate (HR 0.62, 95% CI 0.42-0.93, p=0.022) analysis.

CONCLUSIONS: The present study emphasized that low HRR was a poor prognostic factor for PFS in patients with MPC. There was no statistically significant difference between the HRR groups regarding OS. This is the first study evaluating the prognostic significance of HRR in MPC.

Key Words:

Advanced pancreas cancer, Hemoglobin, Red cell distribution width ratio, Prognosis.

Introduction

Pancreatic cancer (PC) has been shown to have the worst prognosis among cancer types[1,2]. It is the fourth most common cause of cancer-related deaths worldwide[3]. Five-year overall survival is about 1%-17% at all stages[4,5]. PC follows an asymptomatic course in the early stages, therefore vast majority of patients are diagnosed at an advanced stage and systemic chemotherapy may be the only treatment option in the majority of cases[6,7].

It is important to predict the prognosis of pancreatic cancer because of its aggressive course and often presenting at an advanced stage. In clinical practice, a number of achievable and low-cost parameters are investigated. Studies[8-10] have shown that systemic inflammation activation of cancer cells and their microenvironments may be associated with tumor proliferation and metastasis. For this purpose, various studies[11-16] have been conducted to estimate the prognosis, such as neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic immune-inflammatory index, using hemogram parameters routinely examined in cancer patients. Low hemoglobin (HGB) is a component of these parameters and occurs multifactorially[17,18]. Low HGB causes tumor hypoxia. Thus, tumor angiogenesis due to hypoxia increases the tumor's aggressiveness by stimulating it. This situation negatively affects the prognosis[19-22]. For example, it was found that hemoglobin was associated with disease prognosis in various cancer types such as esophageal, gastric, colorectal, and endometrial cancers[23,24]. Red cell distribution width (RDW), which is also among the hemogram parameters, is a value that shows the variability in the volumes of red cells. Increasing evidence suggests that RDW is a diagnostic and prognostic marker in hematological cancers and

Corresponding Author: Ayşegül İlhan, MD; e-mail: ayse_ilhan85@hotmail.com

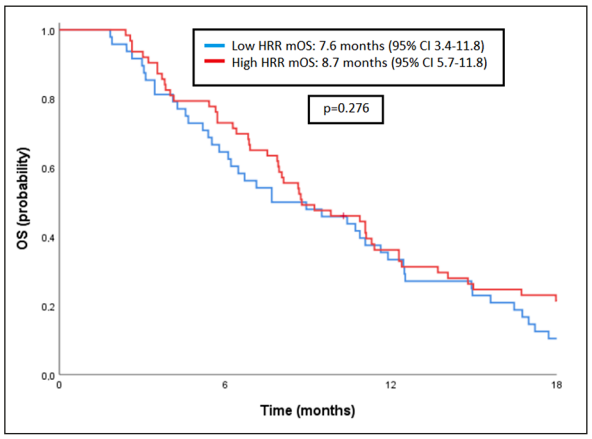

Figure 1. Kaplan–Meier curves for overall survival (OS) according to the HB/RDW ratio.

solid organ tumors[25-27]. However, HGB and RDW parameters are affected by many factors other than malignancy alone. In order to relatively reduce this effect, HBG-RDW ratio (HRR) was determined as a parameter. Recently, it has been found to be a prognostic marker in lung, bladder, head, and neck cancers[28-30]. HBG-RDW ratio has not yet been described in patients with metastatic pancreas cancer.

In our study, we aimed to evaluate the relationship between pre-treatment HRR and progression-free survival (PFS) and median overall survival (mOS) in patients with metastatic pancreas cancer.

Patients and Methods

Patient Characteristics

Metastatic PC patients who were followed and treated between January 2001 and January 2021 were evaluated retrospectively. Ethics approval was obtained from the Ethics Committee of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara/TURKIYE. This study was conducted in concordance with the principles of the Declaration of Helsinki.

Metastatic PC patients aged 18 years or older treated with at least one cycle of chemotherapy were included in the study. Patients with bone marrow infiltration, secondary malignancy, and anemia at the time of diagnosis were excluded from the study.

Medical records of patients were obtained from patient files and an electronic recording system. Pre-treatment HRR was calculated according to the HGB/RDW formula.

Mainly used first-line chemotherapy agents were mFOLFIRINOX (oxaliplatin 85 mg/m^2 on day 1+irinotecan 180 mg/m^2 on day 1+leucovorin 400 mg/m^2 on day 1 followed by FU 400 mg/m^2 as a bolus on day 1 and 2400 mg/m2 as 46h continuous infusion biweekly) or gemcitabinebased (gemcitabine at a dose of 1000 mg/m^2, on days 1, 8, and 15 every 4 weeks alone or with nabpaclitaxel 125 mg/m^2, or gemcitabine at a dose of 1000 mg/m^2, on days 1 and 8 every 3 weeks with cisplatin 75 mg/m^2 on day 1).

Radiological treatment outcome was evaluated according to response evaluation in solid tumors criteria 1.1 (RECIST 1.1).

SFS was defined as the time from initiation of therapy to progression or intolerable/fatal toxicity; OS was defined as the time from diagnosis of metastatic disease to the last visit or death in months.

Statistical Analysis

Statistical Package for Social Sciences (SPSS®) v.23 was used for data analysis (IBM Corp., Armonk, NY, USA). Receiver operating characteristic (ROC) analysis was performed for the most appropriate value to determine the presence of death or progression for HRR. Cut-off values with acceptable sensitivity and specificity could not be achieved in the ROC analysis. Therefore, the mean value of the HRR variable with normal distribution was used. According to the determined mean value, high and low groups were formed for HRR. The groups were compared in terms of PFS at first-line treatment and OS. The Kaplan-Meier method performed survival analyses, and subgroups were compared by log-rank test. The relationship between OS, PFS, patient, tumor characteristics, and treatment were investigated by COX regression analysis, $p<0.05$ was considered statistically significant.

Results

Patient Characteristics and Treatments

A sum of 111 patients who were followed up and treated with metastatic pancreas cancer in our center were included. The median age of the patients was 59 (range= 33-82), 73.0% (n=81) of patients were male and 27.0% (n=30) were female. 22.5% (n=45) of patients were 65 years of

age or older. The most common location was the pancreatic head, 54.1% (n=60). At all, 82.0% (n= 91) of the patients had liver metastasis, and the liver was the most common metastasis site. The main patient and tumor characteristics are shown in Table I.

Mean HRR was calculated as 0.84, and patients were divided into two groups as low HRR (<0.84) and high HRR (≥0.84). 43.2% (n=48) of patients were in the low HRR group and 56.8% (n=63) were in the high HRR group. There was no significant difference between the low HRR and high HRR groups regarding to clinic-pathological features (Table I).

The most common first-line treatment regimen was mFOLFIRINOX [53.2% (n=59)]. The second most frequently given regimen was gemcitabine-based monotherapy or combination treatments. First-line chemotherapy responses were partial response (PR) in 15.3% (n=17) patients, stable disease (SD) in 36.9% (n=41) patients and progressive disease (PD) in 47.7% (n=53) patients. Treatment process and best response rate information are shown in Table II.

Survival Analysis

The median follow-up was 8.7 months (95% CI 1.8-51.6). The median duration of first-line treatment was 4.4 months (95% CI 0.5-31.3). The median OS was 7.6 months (95% CI 3.4-11.8) in the low HRR group and 8.7 months (95% CI 5.7-11.8) in the high HRR group ($p = 0.276$) (Figure 1). The median PFS was 4.2 months (95% CI 2.7-5.6) in the low HRR group and 5.1 months (95% CI 2.8-7.4) in the high HRR group ($p = 0.044$) (Figure 2).

In the univariate analyses, in which we evaluated the factors affecting progression in the first-line treatment, it was found that the variables of being in the metastatic stage at the time of diagnosis (HR=1.9; 95% CI 1.18-3.15, $p = 0.009$), presence of liver metastasis (HR=1.89, were 95% CI 1.10-3.23, $p = 0.019$) increased progression, HRR ≥ 0.84 (HR=0.67, 95% CI 0.45-0.99, $p = 0.046$), and combination chemotherapy at first-line treatment (HR=0.58, 95% CI 0.38-0.90, $p = 0.014$) were reduced progression (Table III). In the multivariate analysis, it was found that being in the metastatic stage at the time of diagnosis

Table I. Demographic characteristics of the patients.

	Total	Low HRR	High HRR	p
Number of patients, n (%)	111 (100%)	48 (43.2%)	63 (56.8%)	
Median age, years (range)	59 (33-82)	61 (35-78)	57 (33-82)	
Elderly, n (%)				0.931
< 65 years old	86 (77.5%)	37 (43.0%)	49 (57.0%)	
≥ 65 years old	25 (22.5%)	11 (44.0%)	14 (56.0%)	
Sex, n (%)				0.082
Female	30 (27%)	17 (56.7%)	13 (43.3%)	
Male	81 (73%)	31 (38.3%)	50 (61.7%)	
ECOG PS, n (%)				0.348
0	21 (18.9%)	11 (52.4%)	10 (47.6%)	
≥ 1	90 (81.1%)	37 (41.1%)	53 (58.9%)	
Metastatic condition at initial diagnosis, n (%)				0.055
Non-metastatic	21 (18.9%)	13 (61.9%)	8 (38.1%)	
Metastatic	90 (81.1%)	35 (38.9%)	55 (61.1%)	
Primary tumor localization, n (%)				
Head	60 (54.1%)	29 (48.3%)	31 (51.7%)	0.240
Body	41 (36.9%)	14 (34.1%)	27 (65.9%)	0.139
Tail	10 (9.0%)	5 (50%)	5 (50%)	0.651
Metastatic region, n (%)				
Liver	91 (82%)	40 (44%)	51 (56%)	0.746
Peritoneum	19 (17.1%)	10 (52.6%)	9 (47.4%)	0.364
Lung	20 (18%)	8 (40%)	12 (60%)	0.746
Others	8 (7.2%)	4 (50%)	4 (50%)	0.689
Number of metastatic regions, n (%)				0.685
< 2	51 (45.9%)	21 (41.2%)	30 (58.8%)	
≥ 2	60 (54.1%)	27 (45%)	33 (55%)	
Chemotherapeutic agent, n (%)				0.343
Single agent	30 (27%)	14 (46.7%)	16 (53.3%)	
Doublet regimen	22 (19.8%)	12 (54.5%)	10 (45.5%)	
Triplet regiment	59 (53.2%)	22 (37.3%)	37 (62.7%)	

Table II. First-line treatment features.

Median duration of treatment, months, (range)		n (%)
Treatment Protocols	mFOLFIRINOX	59 (53.2%)
	Gemcitabine+nab-paclitaxel	5 (4.5%)
	Gemcitabine+Cisplatin	14 (12.6%)
	Gemcitabine	30 (27%)
	FOLFOX	3 (2.7%)
Best Response Rate	Partial Remission	17 (15.3%)
	Stable Disease	41 (36.9%)
	Progressive Disease	53 (47.7%)

(HR=2.28, 95% CI 1.24-4.21, p = 0.008) and presence of liver metastasis (HR = 1.83, 95% CI 1.05-3.31, p = 0.034) were increased progression, HRR ≥ 0.84 (HR=0.62, 95% CI 0.42-0.93, p = 0.022) and combination chemotherapy at first-line treatment (HR=0.46, 95% CI 0.29-0.72, p = 0.001) were decreased progression (Table III).

In the univariate analyses evaluating the factors affecting death, it was found that the presence of peritoneal metastasis increased death (HR=1.67, 95% CI 1.01-2.77, p = 0.045) (Table IV). In the multivariate analysis performed with the peritoneal metastasis variable and the chemotherapy variable considered clinically significant, no statistically significant factor affecting death was detected (Table IV).

Discussion

In our study, we aimed to evaluate the prognostic significance of the pre-treatment HB/RDW ratio in patients with metastatic PC. In the low HRR group, the median PFS was statistically significantly shorter, indicating that low HRR was a poor prognostic factor for PFS at the first-line setting. There was no statistically significant difference between the HRR groups in terms of OS.

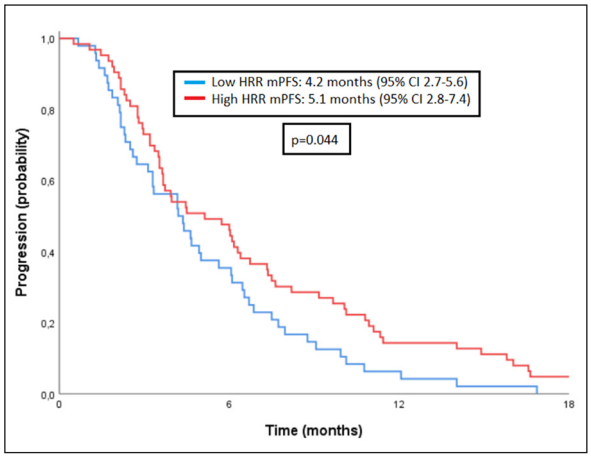

Figure 2. Kaplan–Meier curves for progression-free survival (PFS) according to the HB/RDW ratio.

There are few studies[31-33] investigating the prognostic significance of HRR in cancer patients. It was firstly evaluated by Sun et al[31] in 362 patients with esophageal squamous cell carcinoma[31]. In this study, the optimal cut-off value of HRR for OS was determined as 0.989. The 5-year OS was lower in the low HRR group than in the high HRR group (39.8 months *vs.* 81.7 months, p=0.004), and HRR was found to be an independent prognostic factor for OS. Jiang et al[32] found that pre-treatment low HRR was a poor prognostic marker for OS in 448 patients with advanced non-small cell lung cancer (NSCLC) (HR 1.55, 95% CI 1.17, 2.04). Zhao et al[33] evaluated preoperative HRR in pulmonary large cell neuroendocrine carcinoma in 80 patients. The optimal cut-off value for HRR was determined as 0.969. The low HRR group was shown to have a lower OS than the high HRR group (20.3 months, 95% CI: 14.5 to 26.1 months *vs.* not reached, p<0.001), and low HRR was associated with poor prognosis for OS (HR=3.16, 95% CI: 1.69 to 5.93, p<0.001)[33]. In the three studies mentioned above, HRR was found to be a prognostic factor for OS in different cancer types. Sun et al[31]and Zhao et al[33]included cancer patients with a chance of curable treatment, while Jiang et al[32] evaluated cancer patients in the metastatic stage, similar to our study. In our study, it was observed that low HRR was not a prognostic factor for OS in metastatic pancreas cancer. This result may be due to the more aggressive course of pancreatic cancer compared to cancer types in these three

Table III. Univariate and multivariate analyses results including factors that may affect progression-free survival.

	Univariate			Multivariate		
	HR	CI (%)	p	HR	CI (%)	p
Elderly						
< 65 years old	Ref					
≥ 65 years old	1.15	0.73-1.81	0.528			
Sex						
Female	Ref					
Male	0.97	0.63-1.48	0.898			
ECOG PS						
0	Ref					
≥ 1	1.51	0.94-2.44	0.088			
Metastatic condition at initial diagnosis						
Non-metastatic	Ref					
Metastatic	**1.9**	**1.18-3.15**	**0.009**	**2.28**	**1.24-4.21**	**0.008**
Primary tumor localization						
Head	Ref					
Body	0.79	0.53-1.19	0.274			
Tail	1.74	0.90-3.36	0.095			
Metastatic region						
Liver	**1.89**	**1.10-3.23**	**0.019**	**1.88**	**1.05-3.37**	**0.034**
Peritoneum	1.40	0.83-2.34	0.200	1.50	0.88-2.55	0.132
Lung	0.94	0.57-1.53	0.808	1.51	0.85-2.69	0.154
Others	1.18	0.57-2.44	0.654			
Number of metastatic regions						
< 2	Ref					
≥ 2	1.44	0.99-2.11	0.056			
Chemotherapeutic agent						
Single agent	Ref					
Combination chemotherapy	**0.58**	**0.38-0.90**	**0.014**	**0.46**	**0.29-0.72**	**0.001**
HRR						
< 0.84	Ref					
≥ 0.84	**0.67**	**0.45-0.99**	**0.046**	**0.62**	**0.42-0.93**	**0.022**

studies and the variability caused by patients at different stages or the retrospective origin of the studies.

Yılmaz et al[28] evaluated the prognostic importance of HRR before treatment in 152 patients with muscle-invasive bladder cancer. They determined the cut-off value of HRR as 0.88. They found that low HRR was a prognostic factor for both OS and PFS (HR: 0.232; 95% CI: 0.129-0.417; p=0.000, HR: 0.358; CI: 95%: 0.223-0.574; p=0.000, respectively)[28]. Additionally, the cut-off value of HRR was determined as 0.89 in patients with gastric cancer treated with neoadjuvant FLOT by Yılmaz et al[34]. HRR was shown to be an independent prognostic factor for both disease-free survival (DFS) and OS (p<0.001, p<0.037, respectively)[34]. Bozkaya et al[30] took the cut-off value for HRR as 0.88 in 153 patients diagnosed with advanced non-small cell lung cancer. Low HRR was found to be an independent prognostic factor for both OS (HR 1.607, 95% CI: 1.041-2.480, p = 0.03) and PFS (HR 2.635, 95% CI: 1.667-4.166, p< 0.001)[30]. In terms of the cut-off value of HRR, our study and these three studies seem similar. Wu et al[35] investigated the prognostic value of baseline HRR in 146 small cell lung cancer (SCLC) patients in China. They determined the cut-off value for HRR as 0.985 and found that lower HRR associated with poorer OS and PFS (HR=3.782; 95% CI: 2.151-6.652; p<0.001), (HR=2.112; 95% CI: 1.195-3.733; p<0.001, respectively)[35]. Tham et al[29] from the USA determined the cut-off value of HRR in early stage 205 head and neck cancer patients as 1.017 for OS and 1.037 for event-free survival (EFS). Low HRR was associated with worse EFS (HR=2.02, 95% CI: 1.13-3.61, p= 0.017) than high HRR but was not associated with OS. In our study, similar to the studies mentioned above, HRR was found to be a prognostic factor for PFS in metastatic pancreas cancer.

Table IV. Univariate and multivariate analyses results including factors that may affect overall survival

	Univariate			Multivariate		
	HR	CI (%)	p	HR	CI (%)	p
Elderly						
< 65 years old	Ref					
≥ 65 years old	1.45	0.92-2.29	0.109			
Sex						
Female	Ref					
Male	1.14	0.74-1.76	0.546			
ECOG PS						
0	Ref					
≥1	1.50	0.92-2.44	0.098			
Metastatic condition at initial diagnosis						
Non-metastatic	Ref					
Metastatic	1.55	0.95-2.52	0.074			
Primary tumor localization						
Head	Ref					
Body	0.84	0.55-1.26	0.403			
Tail	1.74	0.91-3.35	0.093			
Metastatic region						
Liver	1.33	0.81-2.19	0.256			
Peritoneum	**1.67**	**1.01-2.77**	**0.045**	1.59	0.94-2.68	0.81
Lung	0.64	0.38-1.07	0.091			
Others	0.90	0.44-1.87	0.792			
Number of metastatic regions						
< 2	Ref					
≥ 2	1.26	0.86-1.85	0.231			
Chemotherapeutic agent						
Single agent	Ref					
Combination chemotherapy	0.66	0.42-1.02	0.065			
HRR						
< 0.84	Ref					
≥ 0.84	0.80	0.54-1.91	0.27	0.79	0.45-1.37	0.404

Limitations

The main limitation of our study was its retrospective nature. Additionally, a relatively small number of patients from a single center was the second important limitation. However, to the best of our knowledge, it was still valuable as the first study evaluating HRR in metastatic pancreas cancer with a poor prognosis.

Conclusions

In conclusion, our study revealed that HRR, which has the potential to be a practical prognostic marker investigated in different cancer types and different stages in the literature, may be an independent prognostic marker in metastatic pancreatic cancer. Of course, larger, multicenter, and prospective designed studies are needed to validate these types of practical and useful prognostic markers with a higher level of evidence.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research received no external funding

Ethics Approval

Ethics Committee of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey (Approval number: 2021-10/1418).

Availability of Data and Material

The data sets and data analyzed in the study are available from the corresponding author on reasonable request.

Authors' Contribution

The study conception and designed was by Mutlu Dogan and Aysegul Ilhan. Statistical analysis was designed and

performed by Fatıh Gurler. Material preparation and data collection were performed by Emrah Eraslan and Funda Cınkıl. The first draft of the manuscript was written by Aysegul Ilhan, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ORCID ID

Aysegul Ilhan: 0000-0002-0333-1388; Fatih Gurler: 0000-0003-0023-5793; Funda Cınkıl: 0000-0002-7409-5730; Emrah Eraslan: 0000-0003-2497-5913; Mutlu Dogan: 0000-0001-9359-3770.

References

1) Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, Gao F. Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J Gastroenterol 2021; 27: 4298-4321.
2) Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol 2021; 18: 493-502.
3) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249.
4) McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2018; 24: 4846-4861.
5) Cai J, Chen H, Lu M, Zhang Y, Lu B, You L, Zhang T, Dai M, Zhao Y. Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. Cancer Lett 2021; 520: 1-11.
6) Chen X, Liu F, Xue Q, Weng X, Xu F. Metastatic pancreatic cancer: Mechanisms and detection (Review). Oncol Rep 2021; 46: 231.
7) Eraslan E, Yildiz F, Tufan G, Aslan F, Demirci U, Oksuzoglu OB. First line modified Folfirinox versus gemcitabine for advanced pancreatic cancer: A single institution retrospective experience. Journal of Oncological Sciences 2019; 5: 1-5.
8) Hainaut P, Plymoth A. Targeting the hallmarks of cancer: towards a rational approach to next-generation cancer therapy. Curr Opin Oncol 2013; 25: 50-1.
9) Kroemer G, Pouyssegur J. Tumor cell metabolism: cancer's Achilles' heel. Cancer Cell 2008; 13: 472-82.
10) Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-74.
11) Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med 2020; 18: 360.
12) Al Jarroudi O, El Bairi K, Abda N, Zaimi A, Jaouani L, Chibani H, Afqir S. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictors of outcomes in inflammatory breast cancer. Biomark Med 2021; 15: 1289-1298.
13) Kim TG, Park W, Kim H, Choi DH, Park HC, Kim SH, Cho YB, Yun SH, Kim HC, Lee WY, Lee J, Kang KM. Baseline neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in rectal cancer patients following neoadjuvant chemoradiotherapy. Tumori 2019; 105: 434-440.
14) Toledano-Fonseca M, Cano MT, Inga E, Gómez-España A, Guil-Luna S, García-Ortiz MV, Mena-Osuna R, De la Haba-Rodriguez JR, Rodríguez-Ariza A, Aranda E. The Combination of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio with Liquid Biopsy Biomarkers Improves Prognosis Prediction in Metastatic Pancreatic Cancer. Cancers (Basel) 2021; 13: 1210.
15) Han R, Tian Z, Jiang Y, Guan G, Sun X, Yu Y, Zhang L, Zhou J, Jing X. Prognostic significance of systemic immune-inflammation index and platelet-albumin-bilirubin grade in patients with pancreatic cancer undergoing radical surgery. Gland Surg 2022; 11: 576-587.
16) Lei H, Xu S, Mao X, Chen X, Chen Y, Sun X, Sun P. Systemic Immune-Inflammatory Index as a Predictor of Lymph Node Metastasis in Endometrial Cancer. J Inflamm Res 2021; 14: 7131-7142.
17) Abdel-Razeq H, Hashem H. Recent update in the pathogenesis and treatment of chemotherapy and cancer induced anemia. Crit Rev Oncol Hematol 2020; 145: 102837.
18) Natalucci V, Virgili E, Calcagnoli F, Valli G, Agostini D, Zeppa SD, Barbieri E, Emili R. Cancer Related Anemia: An Integrated Multitarget Approach and Lifestyle Interventions. Nutrients 2021; 13: 482.
19) Hughes VS, Wiggins JM, Siemann DW. Tumor oxygenation and cancer therapy-then and now. Br J Radiol 2019; 92: 20170955.
20) Bosco MC, D'Orazi G, Del Bufalo D. Targeting hypoxia in tumor: a new promising therapeutic strategy. J Exp Clin Cancer Res 2020; 39: 8.
21) Sebestyén A, Kopper L, Dankó T, Tímár J. Hypoxia Signaling in Cancer: From Basics to Clinical Practice. Pathol Oncol Res 2021; 27: 1609802.
22) Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia (Auckl) 2015; 3: 83-92.
23) Wallace K, Li H, Brazeal JG, Lewin DN, Sun S, Ba A, Paulos CM, Rachidi S, Li Z, Alekseyenko AV. Platelet and hemoglobin count at diagnosis are associated with survival in African American and

Caucasian patients with colorectal cancer. Cancer Epidemiol 2020; 67: 101746.

24) Wei Q, Yuan X, Xu Q, Li J, Chen L, Ying J. Correlation Between Hemoglobin Levels and the Prognosis of First-Line Chemotherapy in Patients with Advanced Gastric Cancer. Cancer Manag Res 2020; 12: 7009-7019.

25) Montagnana M, Danese E. Red cell distribution width and cancer. Ann Transl Med 2016; 4: 399.

26) Hu L, Li M, Ding Y, Pu L, Liu J, Xie J, Cabanero M, Li J, Xiang R, Xiong S. Prognostic value of RDW in cancers: a systematic review and meta-analysis. Oncotarget 2017; 8: 16027-16035.

27) Qin Y, Wang P, Huang Z, Huang G, Tang J, Guo Y, Huang P, Lai Z, Lin F. The value of red cell distribution width in patients with ovarian cancer. Medicine (Baltimore) 2017; 96: e6752.

28) Yılmaz A, Yılmaz H, Tekin SB, Bilici M. The prognostic significance of hemoglobin-to-red cell distribution width ratio in muscle-invasive bladder cancer. Biomark Med 2020; 14: 727-738.

29) Tham T, Olson C, Wotman M, Teegala S, Khaymovich J, Coury J, Costantino P. 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.

30) 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.

31) Sun P, Zhang F, Chen C, Bi X, Yang H, An X, Wang F, Jiang W. 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.

32) Jiang H, Jiang W, Tan L, Yu Q, Liu F, Huang Y, He J, Zhou S. 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. J Int Med Res 2021; 49: 3000605211004229.

33) Zhao W, Shi M, Zhang J. Preoperative hemoglobin-to-red cell distribution width ratio as a prognostic factor in pulmonary large cell neuroendocrine carcinoma: a retrospective cohort study. Ann Transl Med 2022; 10: 42.

34) Yılmaz A, Mirili C, Tekin SB, Bilici M. 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.

35) Wu F, Yang S, Tang X, Liu W, Chen H, Gao H. 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.