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THE RELATIONSHIP BETWEEN RDW AND CLINICAL OUTCOMES IN PATIENTS WITH PANCREATIC CANCER – SINGLE CENTRE EXPERIENCE

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Summary

Objective: The prognostic importance of red cell distribution width (RDW) has been noted in various diseases, however, its clinical significance in patients with pancreatic cancer is unknown. In this retrospective study, we aimed to reveal its prognostic value.

Patients and methods: Patients diagnosed with pancreatic adenocarcinoma from Dec 14, 2017, until Dec 10, 2021, in Clinical Hospital Osijek, were evaluated retrospectively in terms of RDW and its clinical significance on the outcome of the disease.

Results: There were 81 patients, who were divided into normal RDW and high RDW groups. The median follow-up was 61 months. The median duration of first-line treatment was 3 months (95% CI 2-8) and the median duration of second-line treatment was 3 months (95% CI 3-6). The median overall survival was 11 months (95% CI 5-18). Multivariate regression analysis (Stepwise method) along with the adjustment of disease stage shows that higher levels of RDW increase the probability of shorter overall survival (HR=1,13).

Conclusion: There is a paucity of the literature on the prognostic importance of RDW on clinical outcomes in patients with pancreatic cancer. Our study with bivariate-regression analysis (COX) shows that a significant predictor of shorter overall survival is higher level of RDW (HR=1,16)

KEYWORDS: *red cell distribution width, pancreatic neoplasms, clinical relevance*

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDA) is an aggressive malignancy, the 12th most common cancer in the United States with a lifetime risk of 1,5 % and a median age at diagnosis is 70 years(1-4).

The greatest risk factors for pancreatic cancers are strong family history and smoking tobacco. Other risk factors include pancreatitis, obesity and diabetes(1-5).

Pancreatic cancer refers to a heterogeneous group of malignant pathologies that originate in the pancreas and almost all are epithelial in origin. Over 85 % of all malignant pathologies of the pancreas are the conventional pancreatic (tubular) ductal adenocarcinoma(PDA), and more than 98 % of the remaining malignancy fits into one of the following diagnoses: solid types – pancreatic endocrine neoplasm, acinar cell carcinoma, pancreatoblastoma or cystic types – mucinous cystic neoplasm (MCN),

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solid-pseudopapillary neoplasm (SPN), intraductal papillary mucinous neoplasm (IPMNs)(1-5).

Patients with suspected malignancy of the pancreas should undergo a comprehensive history and physical exam focused especially on the abdomen and regional lymph nodes. Jaundice is a common sign of right-sided lesions when the bile duct is obstructed (75% of patients). Other common signs and symptoms include fatigue, pruritus, weight loss, new onset of diabetes, new onset of depression and steatorrhea. Laboratory tests must include liver enzymes, total bilirubin, hemoglobin A1C, glucose, serum albumin and also tumor markers (carcinoembryonic antigen(CEA) and carbohydrate antigen(CA) 19-9). Imaging is performed of the chest, abdomen and pelvis, for staging it may include a high-quality MRI or CT scan. A tissue diagnosis is required of patients starting neoadjuvant or palliative therapy, a biopsy is not mandatory for patients when there is a high suspicion of PDA, and resection is planned as first-line treatment. Pancreatic cancer is staged according to the AJCC eighth edition TNM staging system(1-5).

Surgery is considered the only potentially curative treatment for pancreatic cancer, followed by adjuvant chemotherapy, although it is reserved for a minority of patients. For metastatic pancreatic cancer, chemotherapy remains superior to supportive treatment. First-line chemotherapy regimens for metastatic pancreatic cancer are FOLFIRINOX and gemcitabine plus nab-paclitaxel when patients have good performance status. Gemcitabine remains an option for patients with lower performance status(1-5).

There has always been increased interest in identifying new noninvasive diagnostic and predictive biomarkers from various hematological and serological parameters(4,6).

Red-cell volume distribution width (RDW) is based on the width of the red-blood-cell volume distribution curve (RDW), which reflects changes in the size of circulating red blood cells. The change in RDW is related to changes in the erythrocyte survival pattern, which indicates the derailment of erythropoiesis. RDW, the main descriptive parameter of erythrocyte variation, is associated with poor prognosis in some diseases. Previous studies have shown that the RDW may have diagnostic and prognostic value for various tumor types, including lung cancer, liver cancer, prostate cancer, esophageal cancer and chronic lymphocytic leukemia. However, the effects of the initial RDW assessment at diagnosis of the of pancreatic cancer on patient prognosis have rarely been reported, and there is a lack of literature focusing on RDW in the setting of pancreatic cancer(5-7).

In Croatia, there were 428 new cases in males and 437 new cases in females in 2020. The incidence of pancreatic ductal adenocarcinoma was 19.6, with a mortality rate of 17.8, highlighting pancreatic cancer as one of the most lethal diseases in the country. Although death rates of the most common cancers have generally declined over the past 80 years, PDA death rates remain flat or slightly increased over time. Globally, PDA remains a deadly disease with a low curable population of patients(1-5,19,20,21).

The purpose of this study was to investigate the association between the initial assessment of RDW and the overall survival of patients diagnosed with PDA receiving treatment at the Clinical Hospital Centre in Osijek.

MATERIAL AND METHODS

Patient characteristics

The study included patients whose data were retrived from the medical archive at the oncology department of Clinical Hospital Osijek. The data on patients' deaths were obtained from the Registry Office of the Republic of Croatia. Subjects of this retrospective study were 81 patients who underwent treatment in Clinical Hospital Osijek from Dec 14, 2017, until Dec 10, 2021, January 30, 2023, was set as the last date of data monitoring. They were aged 18 years or older.

Mainly used first-line chemotherapy regimens were gemcitabine-based with nabpaclitaxel and FOLFIRINOX.

In our study, the inclusion criteria were: patients who underwent treatment and diagnosis in the Oncology Department of Clinical Hospital Osijek, patients aged 18 years or older, and patients who have undergone laboratory tests in our hospital.

The research was approved by the Ethics Committee of University Hospital Centre Osijek (number of acceptance: R1-4012/2023) and was conducted in accordance with all the principles of the Declaration of Helsinki, ensuring patient ano-

nymity and data confidentiality. Informed consent was not obtained from participants included in the study since data were collected retrospectively from the archive and the information system of University Hospital Centre Osijek.

Statistical Analysis

Categorical data are represented by absolute and relative frequencies. Differences in categorical data were tested with the χ^2 test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. Numerical data are described by the median and the limits of the interquartile range. Differences in numerical variables between two independent groups were tested with the Mann-Whitney test. Cox (bivariate and multivariate). Regression analysis was used to predict the probability of a negative outcome and was expressed as a hazard ratio (HR) and 95% confidence interval (95% CI). Kaplan-Meier survival curves were compared using the log-rank test. All P values are two-sided. The significance

Table 1.

Demographic characteristics of the patients

		min – max
Sex [n (%)]		
M	34 (42)	
F	47 (58)	
Median age,years [Median (IQR)]	68 (62 – 75)	43 – 87
Stage of the disease at initial diagnosis [n (%)]		
I	6 (7)	
II	1 (1)	
III	12 (15)	
IV	62 (77)	
Surgical treatment [n (%)]	18 (22)	
Biochemical indicators [Median (IQR)]		
Erythrocytes	4,1 (3,8 – 4,6)	1,9 – 6,4
Hemoglobin	122 (107,5 – 136,5)	56 – 157
RDW	13,9 (13,3 – 15,6)	11,9 – 22,6
Leukocyte	8,4 (6,4 – 10,4)	0,4 – 31,8
Platelets	226 (181 – 288)	121 – 486
CEA	7,8 (2,7 – 26,8)	0,5 – 465
CA 19-9	568,9 (71,2 – 4480)	0,6 – 172688
RDW [n (%)]		
9 – 15 %	56 (69)	
> 15%	25 (31)	
Adjuvantn therapy	17 (21)	
Chemotherapy	15/ 17	
Radiotherapy	1 / 17	
Chemotherapy + radiotherapy	1 / 17	
Metastasis	70 (86)	
Localization of metastasis		
Liver	49 (61)	
Lymph nodes	20 (25)	
Bones	6 (7)	
Suprarenal glands	3 (4)	
Peritoneum	10 (12)	
Lungs	11 (14)	
Pleural effusion	1 (1)	
Ascites	3 (4)	
Spleen	1 (1)	
Cutaneous metastases	1 (1)	
Ovary	1 (1)	

level was set at Alpha (α) = 0.05. The statistical program MedCalc® Statistical Software version 20.215 is used for statistical analysis. (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023) i SPSS 23 (IBM Corp. Released 2015. Armonk, NY: IBM Corp.).

RESULTS

Patient Characteristics and Treatments

The research was conducted on 81 patients who were treated at Clinical Hospital Centre Osijek. The median age of the patients was 68 (range 62-75), 58% (n=47%) of patients were female and 42% (n=34) were male.

At the initial diagnosis, 77% (n=62) of patients had metastatic disease, while the remaining 23% (n=19) had locoregional disease. Eighteen patients with locoregional disease had undergone surgery and one patient had refused surgery. After surgery 15 of them received adjuvant chemotherapy, 1 patient received only radiation therapy, 1 patient combined adjuvant chemotherapy and radiation therapy and 1 patient from the initial 18 refused therapy. Out of 19 patients who had the locoregional disease, 8 of them eventually developed metastases, others were lost to follow-up. The most common locations of metastasis were the liver 61% (n=61) and lymph nodes 25% (n=25). The main patients and tumor characteristics are presented in Table 1.

The most common first-line treatment regimen was gemcitabine in combination with nabpaclitaxel, the second most frequently given regimen was FOLFIRINOX.

The regimen with a median duration is presented in Table 2.

The normal reference range of RDW in our hospital was from 9 to 15 %, and the median of RDW was 13,9 (CI 13,3-15,6). We have divided patients based on normal and abnormal (> 15%) RDW in 2 groups, presented in Tables 3 and 4. Statistical analysis revealed no significant difference in the time from diagnosis of metastatic disease to death

Table 2.

Duration of treatment

		min – max
1. line of treatment [n (%)]	n = 54 (67 %)	
gemcitabine/nabpaclitaxel	32 (59)	
folfirinox	9 (17)	
gemcitabine	10 (19)	
capecitabine	3 (6)	
Duration of 1. line of treatment (months) [Median (IQR)]	3 (2 – 8)	0,2 – 35
2. line of treatment [n (%)]	n = 18 (22 %)	
gemcitabine/nabpaclitaxel	1 (6) / 18	
folfirinox	8 (44) / 18	
gemcitabine	1 (6) / 18	
capeiri	6 (32) / 18	
capecitabine	1 (6) / 18	
folfiri	1 (6) / 18	
Duration of 2. line of treatment[Medijan (IQR)]	3 (2 – 6)	0,2 – 10
3. line of treatment [n (%)]	n = 8 (10 %)	
folfirinox	2 / 8	
gemcitabine	2 / 8	
capeiri	2 / 8	
capecitabine	2 / 8	
Duration of 3. line of treatment [Medijan (IQR)]	2 (0,5 – 3)	0,2 – 4

		min – max
Time from diagnosis of metastatic disease to death (months) [Medijan (IQR)]	6 (3 – 12)	0,04 – 38
OS (months) [Medijan (IQR)]	11 (5 – 18)	0,07 – 61
Alive	13 (16)	
Died	68 (84)	

based on RDW values, nor were there significant differences in patient characteristics based on RDW.

Survival Analysis

The median follow-up was 61 months. The median duration of first-line treatment was 3 months (95% CI 2-8), the median duration of second-line treatment was 3 months (95% CI 3-6), the median duration of third-line treatment was 2 months (95% CI 0,5-3).

Bivariate – regression analysis (Cox) shows that significant predictors of shorter overall survival (os) are III (HR=5,7) and IV (HR=8,3) disease stage, higher levels of RDW (HR=1,16), the presence of metastasis (HR=2,89), patients without surgical (HR=0,46) and adjuvant treatment (HR=0,45) as well as lower levels of erythrocytes (HR=0,73) and hemoglobin (HR=0,98)(table 6).

Multivariate regression analysis (Stepwise method) along with the adjustment of disease

Table 3.

Characteristics of the patients based on RDW

	number (%) of patients based on RDW			P*
	9 % – 15 %	> 15 %	Total	
Sex				
M	23 (41)	11 (44)	34 (42)	0,81
F	33 (59)	14 (56)	47 (58)	
Stage of the disease at initial diagnosis				
I / II	6 (11)	1 (4)	7 (9)	0,26
III	6 (11)	6 (24)	12 (15)	
IV	44 (79)	18 (72)	62 (77)	
Surgical treatment	14 (25)	4 (16)	18 (22)	0,37
Adjuvant therapy	12 (22)	5 (20)	17 (21)	0,85
Metastasis	51 (91)	19 (76)	70 (86)	0,09
Localization of metastasis				
liver	36 (71)	13 (68)	49 (70)	0,86
Lymph nodes	13 (26)	7 (39)	20 (29)	0,28
peritoneum	7 (14)	3 (17)	10 (15)	0,71
Lungs	7 (14)	4 (22)	11 (16)	0,46
Outcome				
alive	10 (18)	3 (12)	13 (16)	0,75
died	46 (82)	22 (88)	68 (84)	

*χ^2 test

Table 4.

Differences in values with regard to RDW

	Median (interquartile range)		Difference	95% CI	P*
	9 % – 15 %	> 15 %			
Age at initial diagnosis	68 (62 – 76)	70 (64 – 74)	2	-3 do 6	0,52
Biochemical indicators					
Erythrocytes	4,3 (4,0 – 4,7)	3,9 (3,0 – 4,3)	-0,5	-0,86 to -0,16	0,003
Hemoglobin	127 (118 – 141)	105 (91 – 120)	-21	-31 to -12	<0,001
Leukocyte	7,9 (6,4 – 10,1)	10,0 (6,9 – 13,2)	1,5	-0,3 to 3,6	0,09
Platelets	220 (177 – 283)	239 (190 – 360)	27	-11 to 70	0,18
CEA	8 (2,4 – 28)	7,8 (3,2 – 14,9)	-0,2	-7,2 to 4,1	0,92
CA 19-9	873 (55,3 – 5794)	534 (94,9 – 2390,3)	-10,9	-1584 to 291,4	0,79
Time from diagnosis of metastatic disease to death	8,0 (4,5 – 11)	5,0 (1,8 – 12,5)	-2	-5 to 1	0,19

CI – confidence interval; Mann Whitney U test

stage shows that higher levels of RDW increase the probability of shorter overall survival (HR=1,13) (table 7).

We have shown the Kaplan Meier curve for survival probability according to the RDW, the impact of RDW on one-year, two-year and three-year survival probability.

DISCUSSION

Pancreatic cancer stands out as one of the most lethal forms of cancer, often diagnosed at advanced stages, contributing to its high morbidity rates.

The goal of our study was to determine the prognostic significance of the pre-treatment RDW in patients with pancreatic adenocarcinoma. There is a paucity of studies investigating the prognostic significance of RDW in pancreatic cancer patients.

Red cell distribution width (RDW) is an index of the variability in the size of the circulating red blood corpuscles and it is reported routinely. There are very few studies that have been focused on RDW as a marker of prognosis or cancer outcome in various diseases. In the retrospective study conducted by Pradeep et al that showed an association between RDW and tumor stage in patients with resected cancer of the head of the pancreas, patients with lower RDW values had a significantly higher duration of survival(6,18).

In the Tromsø Study, which evaluated the impact of RDW on the future risk of cancer, it has been shown that there is a dose-dependent rela-

Table 5.

Bivariate Cox regression analysis

Bivariate Cox regression analysis	ß	P	HR	95% CI
sex (F)	0,11	0,66	1,12	0,68 to 1,82
age	0,02	0,17	1,02	0,99 to 1,05
Stage of disease				
III	1,74	0,03	5,7	1,22 to 26,3
IV	2,11	0,004	8,3	2,0 to 34,4
Surgical treatment	-0,77	0,01	0,46	0,25 to 0,85
Erythrocytes	-0,32	0,04	0,73	0,53 to 0,99
Hemoglobin	-0,01	0,01	0,98	0,98 to 0,99
RDW	0,15	0,01	1,16	1,04 to 1,30
RDW (range 9 – 15%)				
above 15 %	0,43	0,10	1,54	0,92 to 2,57
Leukocyte	0,03	0,29	1,03	0,97 to 1,09
Platelets	-0,001	0,82	0,99	0,99 to 1,002
CEA	0,0001	0,94	1,001	0,99 to 1,004
CA 19-9	0	0,06	1,00	1,00 to 1,00
Adjuvant treatment	-0,80	0,01	0,45	0,24 to 0,84
Metastasis	1,06	0,02	2,89	1,16 to 7,21
Liver	0,45	0,11	1,57	0,89 to 2,75
Lymph nodes	0,06	0,85	1,06	0,60 to 1,85
Peritoneum	-0,68	0,09	0,51	0,24 to 1,09
Lungs	0,55	0,12	1,74	0,87 to 3,47

ß – regression coefficient

Table 6.

Multivariate regression analysis (Stepwise method)

	ß	P	HR	95% CI
RDW	0,13	0,03	1,13	1,01 to 1,28

Table 7.

Overall survival – Kaplan Meier

	Number (%) of deaths	Number (%) of survived	Total	Survival (%)	Arithmetic mean (months) 95% CI	Logrank test (P)
Overall survival(OS) (61 months of follow up)	68 (84)	13 (16)	81	9%	16,6 (13 – 21)	–
Annual	42 (52)	39 (48)	81	48%	32,3 (26 – 38)	–
Biannual	63 (78)	18 (22)	81	21%	19,6 (15 – 24)	–
Three-year	66 (81)	15 (19)	81	15%	17,8 (13 – 22)	–
Overall survival(OS)						
Stage I / II	2 (29)	5 (71)	7	71%	48,1 (33 – 64)	
Stage III	10 (83)	2 (17)	12	11%	14,2 (10 – 19)	0,002
Stage IV	56 (90)	6 (10)	62	3%	12,7 (9 – 16)	
Overall survival(OS)						
Without metastasis	5 (45)	6 (55)	11	53%	34,4 (19 – 50)	0,02
With metastasis	63 (90)	7 (10)	70	5%	14,2 (11 – 18)	
Overall survival(OS)						
Without surgical treatment	55 (87)	8 (13)	63	4%	13,0 (10 – 16)	0,01
With surgical treatment	13 (72)	5 (28)	18	9 %	27,2 (13 – 21)	
Overall survival(OS)						
RDW in reference range	46 (82)	10 (18)	56	12 %	18,6 (14 – 24)	0,10
RDW >15 %	22 (88)	3 (12)	25	0 %	11,3 (7 – 16)	
Overall survival(OS) – annual						
RDW in reference range	27 (48)	29 (52)	56	55 %	34,9 (28 – 42)	0,09
RDW >15 %	15 (60)	10 (40)	25	40%	16,4 (10 – 23)	
Overall survival(OS) – biannual						
RDW in reference range	43 (77)	13 (23)	56	22 %	21 (15 – 27)	0,22
RDW >15 %	20 (80)	5 (20)	25	18 %	12 (7 – 17)	
Overall survival(OS – three-year						
RDW in reference range	44 (79)	12 (21)	56	20 %	20 (15 – 26)	0,10
RDW >15 %	22 (88)	3 (12)	25	0 %	11 (7 – 16)	

tion between RDW and the future risk of cancer in men and women of postmenopausal age(7).

In a review article by Montagnana and Danese, five studies investigating the prognostic value of RDW in esophageal cancer have been reviewed. All studies were retrospective with quite a long follow-up period and a good sample size. All of them evaluated the prognostic value of preoperative RDW levels since all patients underwent potentially curative resection in association or not with radio and/or chemotherapy. They all applied similar cut-off values ranging from 12,2 % to 15,3 % for dividing patients into high and low RDW categories, only the group of Sun P. And Chen GP showed the optimal cut-off value for RDW by receiver operating characteristic (ROC) curves(8-10) while the others set the values on the upper limit of the reference range used in routine laboratory analyses.

In our study we set the range as the upper limit of the reference range of RDW in our hospital laboratory (reference range 9-15%), which somewhat limits this study.

Motagnana and Danese also showed the results of the mulltivariate analyses which implicated RDW as an independent predictor of patient overall survival and cancer-specific survival. In our study with bivariate – regression analysis (Cox), we showed that significant predictors of shorter overall survival (os) were the higher stage of disease, higher levels of RDW (HR=1,16), the presence of metastasis (HR=2,89), patients without surgical (HR=0,46) and adjuvant treatment

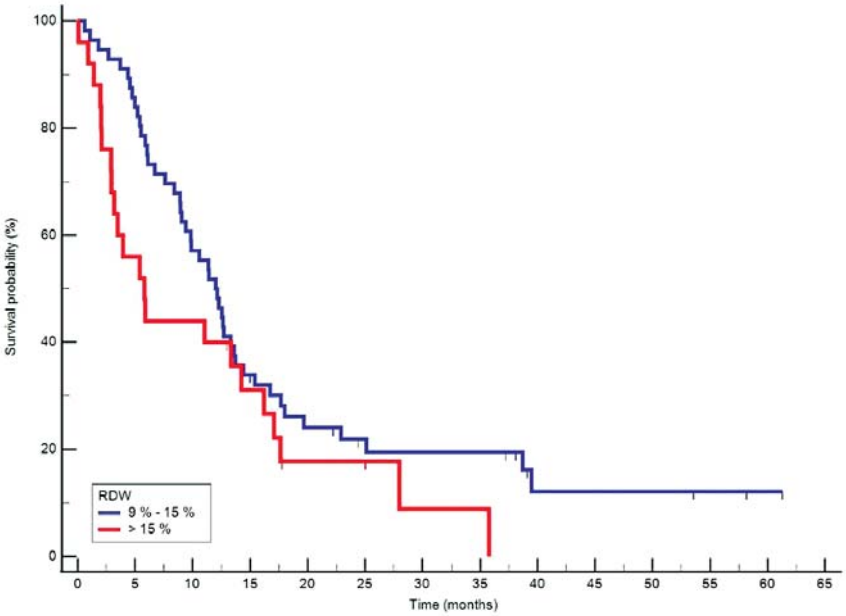

Figure 1. Kaplan-Meier curve for surival probabillity according to the RDW

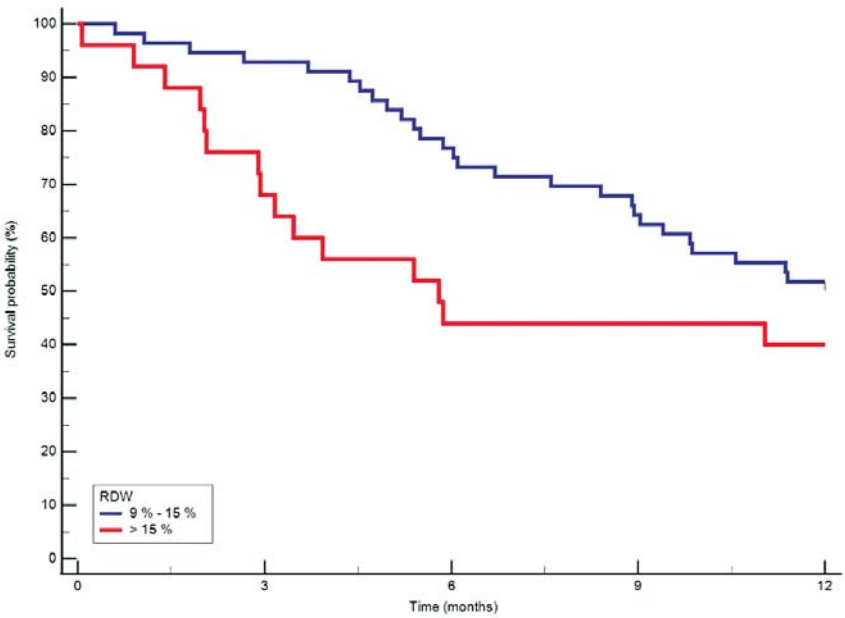

Figure 2. Kaplan-Meier curve for impact of RDW on one-year survival

(HR=0,45) as well as lower levels of erythrocytes (HR=0,73) and hemoglobin (HR=0,98)(8-10,23).

In the study of Sun (8) the crude RDW showed no significant association with OS; the combination of RDW and HB values in the form of hemoglobin/red blood cell distribution ratio was found independently associated with overall survival. Also, Hirahara and colleagues found that high RDW is potentially an independent risk factor for a worse prognosis in non-elderly patients(11,24,25).

In a systematic review and a meta-analysis conducted by Hu et al., which included 17 studies with a total of 4267 patients, it has been shown that elevated RDW significantly predicted poor overall survival, poor cancer-specific survival,

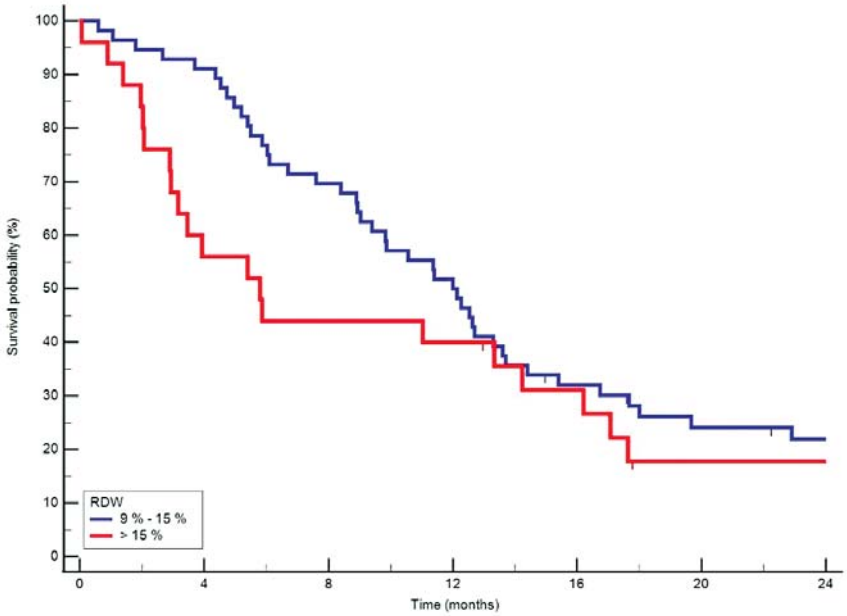

Figure 3. Kaplan-Meier curve for impact of RDW on two-year survival

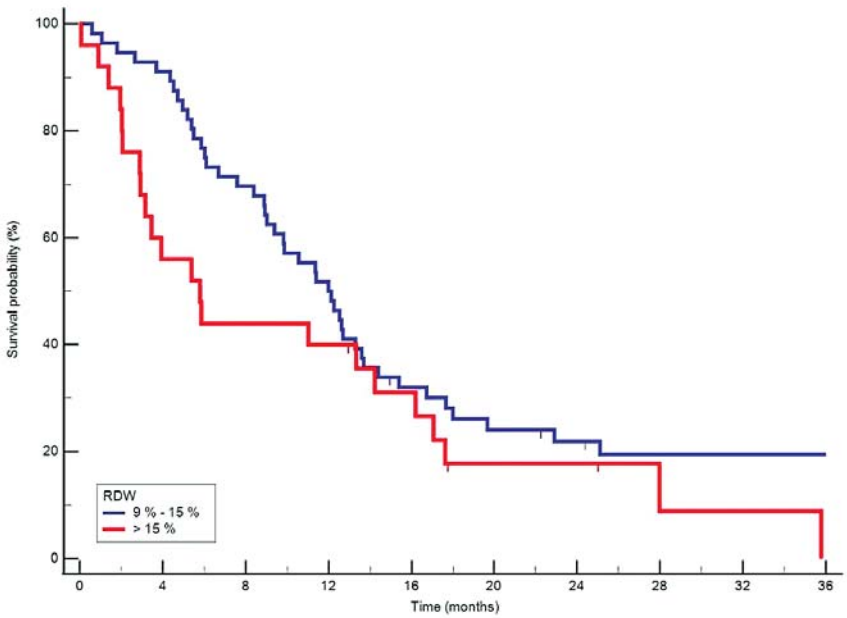

Figure 4. Kaplan-Meierov curve for impact of RDW on three-year survival

poor disease-free survival, poor event-free survival and poor progression-free survival In our study with multivariate regression analysis (Stepwise method) along with the adjustment of disease stage, we showed that higher levels of RDW increased the probability of shorter overall survival (HR=1,13)(12-17,24).

LIMITATIONS

The main limitation of our study was its retrospective design, setting the cut-off value of RDW without using operating characteristic (ROC) curves and small number of patients from a single centre.

CONCLUSION

In conclusion, in our study with multivariate regression analysis (Stepwise method) with the adjustment of disease stage, it has been revealed that higher levels of RDW increase the probability of shorter overall survival. Unfortunately, due to a paucity of literature on prognostic importance of RDW in clinical outcomes of pancreatic cancer, further prospective and larger multicentric studies are required to establish the role of RDW as a biomarkerof a clinical outcome.

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Sažetak

POVEZANOST KOEFICIJENTA VARIJACIJE DISTRIBUCIJE VOLUMENA ERITROCITA (RDW) I UKUPNOG PREŽIVLJENJA KOD PACIJENATA OBOLJELIH OD METASTATSKOG KARCINOMA GUŠTERAČE – ISKUSTVO JEDNOG CENTRA

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Karcinom gušterače povezan je s mnogim etiološkim čimbenicima kao što su debljina, dijabetes, akutni i kronični pankreatitis. Oko 90 % svih tumora gušterače čini duktalni adenokarcinom s prosječnom dobi pri postavljanju dijagnoze od 65 godina te se smatra kako će uskoro postati vodeći uzrok smrti u zapadnim zemljama.U Hrvatskoj u 2020. bilo je 428 novih slučajeva kod muškaraca i 437 novih slučajeva kod žena, sama incidencija iznosila je 19,6 %, a mortalitet 17,8 %. Na Zavodu za onkologiju, KBC Osijek provedena je studija retrospektivnog karaktera na 81 pacijentu koji su se liječili zbog adenokarcinoma gušterače od 14. 12. 2017 do 10. 12. 2021. te je istražen utjecaj koeficijenta varijacije distribucije volumena eritrocita(RDW) i njegovog kliničkog značaja za ishod bolesti. Bivarijatnom regresijskom analizom (Cox) značajni prediktori kraćeg preživljenja u našoj studiji su III (HR = 5,7) i IV (HR = 8,3) stadij bolesti, više vrijednosti RDW (HR = 1,16), prisutne metastaze (HR = 2,89), te bolesnici bez kirurškog (HR = 0,46) i bez adjuvantnog liječenja (HR = 0,45) kao i niže vrijednosti eritrocita (HR = 0,73) i hemoglobina (HR = 0,98). Multivarijatnom regresijskom analizom (Stepwise metoda) uz korekciju stadija bolesti, više vrijednosti RDW povećavaju vjerojatnost manjeg preživljenja (HR = 1,13).

KLJUČNE RIJEČI: *koeficijent varijacije distribucije volumena eritrocita(RDW), tumor gušterače, klinička relevantnost*